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der Vetsuisse-Fakultät Universität Zürich

Direktorin: Prof. Dr. Anja Kipar

Arbeit unter wissenschaftlicher Betreuung von Prof. em. Dr. med. vet. Andreas Pospischil

Swiss Canine Cancer Registry: a Retrospective Study on the Occurrence of Tumours and the Influence of Age, Breed, Body Size, Sex and Castration Status on Tumour Development in Dogs in Switzerland from 1955–2008

Inaugural - Dissertation

zur Erlangung der Doktorwürde der
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vorgelegt von

Katrin Grüntzig

Tierärztin

aus Heidelberg, Deutschland

genehmigt auf Antrag von

Prof. em. Dr. med. vet. Andreas Pospischil, Hauptreferent

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Abstract

This retrospective study presents the Swiss Canine Cancer Registry, containing pathology diagnostic records compiled between 1955 and 2008 by three veterinary diagnostic laboratories in Switzerland. The data set was investigated systematically covering various points of interest. The results were published in two articles in the Journal of Comparative Pathology. The first article (The Swiss Canine Cancer Registry: a retrospective study on the occurrence of tumours in dogs in Switzerland from 1955 – 2008) presents a broad overview on the whole data set. In the second article (Swiss Canine Cancer Registry 1955 – 2008: Occurrence of the most common tumour diagnoses and influence of age, breed, body size, sex and castration status on tumour development) tumours were investigated in small groups for a better comparison with other canine cancer registries and clinical relevance. Analyses of the influence of age, breed, body size, sex and castration status on dogs' tumour development were carried out using multiple logistic regression. The sample size allows detailed insight into the influences of age, breed, body size, sex and castration status on canine tumour development. It is hoped that this study marks the beginning of continuous registration of dog tumours in Switzerland, which will serve as a reference for research in the fields of animal and human oncology.

Keywords: tumour, dog, cancer registry, statistical risk analyses

Zusammenfassung

In dieser retrospektiven Studie wurde das Schweizer Hundekrebsregister erstellt und ausgewertet, dessen zu Grunde liegenden Diagnoseberichte aus drei Veterinärpathologischen Instituten in der Schweiz und dem Zeitraum von 1955 bis 2008 stammen. Die Ergebnisse der Auswertungen wurden in zwei Artikeln im Journal of Comparative Pathology veröffentlicht. Der erste Artikel (The Swiss Canine Cancer Registry: a retrospective study on the occurrence of tumours in dogs in Switzerland from 1955 – 2008) gewährt einen breiten Überblick über das Tumorvorkommen bei den Schweizer Hunden. Im zweiten Artikel (Swiss Canine Cancer Registry 1955 – 2008: Occurrence of the most common tumour diagnoses and influence of age, breed, body size, sex and castration status on tumour development) wurden die Tumoren zu Gunsten besserer Vergleichbarkeit und klinischer Relevanz in differenzierten Untergruppen untersucht. Mittels multipler logistischer Regressionsanalysen wurde der Einfluss von Alter, Rasse, Körpergrösse, Geschlecht und Kastrationsstatus auf die Entwicklung der Tumoren untersucht. Die grosse Datenmenge erlaubte detaillierte Einsichten über die Einflüsse dieser Variablen auf die Tumorentwicklung.

Es ist wünschenswert, dass diese Dissertation das Fundament für ein fortlaufendes Schweizer Hundekrebsregister bildet und weiteren Forschungsarbeiten im Gebiet der Onkologie für Mensch und Tier als Grundlage dient.

Stichworte: Tumor, Hund, Krebsregister, statistische Risikoanalysen

The Swiss Canine Cancer Registry: a retrospective study on the occurrence of tumours in dogs in Switzerland from 1955 – 2008

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NEOPLASTIC DISEASE

The Swiss Canine Cancer Registry: A Retrospective Study on the Occurrence of Tumours in Dogs in Switzerland from 1955 to 2008

K. Grüntzig[*], R. Graf[*], M. Hässig[†], M. Welle[‡], D. Meier[§], G. Lott[¶], D. Erni[#], N. S. Schenker[¶], F. Guscetti[¶], G. Boo[‖], K. Axhausen[††,*], S. Fabrikant[††], G. Folkers[*] and A. Pospischil[¶,*]

**Collegium Helveticum, Universität Zürich und Eidgenössische Technische Hochschule Zürich (ETHZ), [†]Departement Nutztiere Universität Zürich, Zurich, [‡]Institut für Tierpathologie Universität Bern, Bern, [§]Zyto-Histo Diagnostics, Freienstein, [‖]Geographisches Institut, Universität Zürich, [¶]Institut für Veterinärpathologie Universität Zürich, Zurich, [#]FocusedPublishing GmbH, CH-8332 Russikon and [††]Institut für Verkehrsplanung und Transportsysteme (IVT), ETHZ, Zurich, Switzerland*

Summary

Diagnostic records are a key feature of any cancer epidemiology, prevention or control strategy for man and animals. Therefore, the information stored in human and animal cancer registries is essential for undertaking comparative epidemiological, pathogenic and therapeutic research. This study presents the Swiss Canine Cancer Registry, containing case data compiled between 1955 and 2008. The data consist of pathology diagnostic records issued by three veterinary diagnostic laboratories in Switzerland. The tumours were classified according to the guidelines of the International Classification of Oncology for Humans on the basis of tumour type, malignancy and body location. The dogs were classified according to breed, age, sex, neuter status and place of residence. The diagnostic data were correlated with data on the Swiss general dog population and the incidence of cancer in dogs was thus investigated. A total of 67,943 tumours were diagnosed in 121,963 dogs and 47.07% of these were malignant. The most common tumour location was the skin (37.05%), followed by mammary glands (23.55%) and soft tissue (13.66%). The most common tumour diagnoses were epithelial (38.45%), mesenchymal (35.10%) and lymphoid tumours (13.23%). The results are compared with data in other canine registries and similarities in tumour distribution and incidence are noted. It is hoped that this study will mark the beginning of continuous registration of dog tumours in Switzerland, which, in turn, will serve as a reference for research in the fields of animal and human oncology.

Keywords: cancer registry; dog; epidemiology

Introduction

Cancer is a leading cause of death in man and dogs (Pinho *et al.*, 2012); however, current medical research is hampered by the complex biology of the disease. Murine cancer models are highly standardized and have contributed tremendously to knowledge of cancer mechanisms and treatment regimes, but such models are often limited in representing specific aspects of spontaneously arising human cancer such as long time latency, recurrence and metastasis (Porello *et al.*, 2006; Thamm and Dow, 2009; Martić-Kehl *et al.*, 2012; Ranieri *et al.*, 2013). Such information is best derived from cancer registries, which provide data on the epidemiology of cancer over space and time. In many countries, human cancer registration has been practiced since the 1940s (Brønden *et al.*, 2007).

Companion animal cancer registries were introduced in the 1960s, following increasing mortality

Correspondence to: A. Pospischil (e-mail: apos@vetpath.uzh.ch).

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due to spontaneously arising tumours. The study of companion animal tumours offers benefits not only for animal epidemiology, but also for comparative epidemiological, pathogenic and therapeutic research. Companion animals have a life span that allows them to develop tumours resembling equivalent human cancers in their morphology and biological behaviour. Companion animals also benefit from oncological therapies that are used in human medicine. Companion animals share the same environment as their owners and can therefore act as sentinels for recognition of environmental factors implicated in oncogenesis (Bukowski and Wartenberg, 1997; Backer *et al.*, 2001; Gamlem *et al.*, 2008; Marconato *et al.*, 2009; Bettini *et al.*, 2010). Companion animals, and dogs in particular, share significantly more of their genome with man than do rodents (Pinho *et al.*, 2012). Therefore, investigations of spontaneously arising cancer in dogs can provide a partial alternative to animal testing (Bukowski and Wartenberg, 1997; Thamm and Dow, 2009).

In the 1960s and 1970s three population-based animal registries were reported in the USA: the California Animal Neoplasm Registry (1963–1966; Dorn, 1967), the Kansas University Neoplasm Registry (1961–1971; Strafuss, 1976) and the Tulsa Registry of Canine and Feline Neoplasms (1972–1977; MacVean *et al.*, 1978). Since the late 1980s several animal cancer registries have been established and are still being updated: the Purdue Comparative Oncology Program (since 1979; Purdue Comparative Oncology Program, 2006), the Cancer Registry and Surveillance System for Companion Animals, Cornell (since 1980; Page, 2004), the Animal Tumour Registry of Genoa (since 1985; Merlo *et al.*, 2008), the Norwegian Cancer Project (since 1990; Gamlem *et al.*, 2008), the VetCancer Registry (since 1994; Brønden *et al.*, 2007), the Registry on Canine Tumours in Sweden/Agria (since 1995; Egenvall *et al.*, 2011), the Danish Veterinary Cancer Registry (since 2005; Brønden *et al.*, 2010), the Animal Tumour Registry of the Vicenza and Venice provinces (since 2009; Vascellari *et al.*, 2009) and the Guelph Companion Animal Cancer Epidemiologic Registry (since 2010; Nødtvedt *et al.*, 2011).

The Swiss Canine Cancer Registry (1955–2008) was assembled as part of the project 'One Medicine – One Oncology: Incidence and Geographic Distribution of Companion Animal Cancer in Switzerland, 1955–2008'. Additionally, the project benefits from information about the general canine population at risk, since microchipping and registration of dogs in Switzerland has been compulsory since 2006. The general dog population was surveyed with an accuracy reaching 95% in 2008 (personal information, Gesellschaft Schweizer Tierärztinnen und Tierärzte, the Swiss Society of Veterinarians). These latest data, together with data originating from previous research on the Swiss general dog population, allows data in the registry to be analysed against the background of the total population of dogs in Switzerland (Pospischil *et al.*, 2013).

The aim of this paper is to present the Swiss Canine Cancer Registry, which was compiled between 1955 and 2008. Data consists of pathology diagnostic records issued by three veterinary diagnostic laboratories in Switzerland. The tumours were classified according to the guidelines of the International Classification of Oncology for Humans (ICD-O-3) on the basis of tumour type, malignancy and body location (WHO, 2013). The dogs were classified according to breed, age, sex, neuter status and place of residence. The analysis provides a retrospective overview of the incidence of malignant and benign neoplasms in the Swiss canine population. The findings are related to the general dog population and the tumours are characterized by type, biological behaviour, body location, age of animal and diagnostic method.

Materials and Methods

Data Source

The dog tumour registry comprises 121,963 diagnostic records provided by three veterinary diagnostic laboratories in Switzerland: the Vetsuisse Faculty, Institut für Veterinärpathologie, Zürich (IVPZ), the Institut für Tierpathologie, Bern (ITP) and the Zyto-Histo Diagnostics private veterinary diagnostic laboratory (based in Rorbas Freienstein).

The IVPZ provided three sets of diagnostic records (n = 97,759; 1955–2008) from canine post-mortem, biopsy and cytology samples. The datasets originated from three time periods during the history of this institution. The IVPZ-GL (1955–1964) provided 3,797 records from canine post-mortem samples. These records were originally handwritten documents that were later digitized in an Excel file. The IVPZ-SLK (1964–1988) provided 33,100 records from canine post-mortem and biopsy samples. These records were originally transcribed onto punch cards using diagnostic key words (Keydex, Fa. Royal McBee; Stünzi and Lott-Stolz, 1967) and were digitized by Scydoc, an external company based in Zug, Switzerland. The results were crosschecked using the original typed reports. The IVPZ-APPX (1987–2008) provided 60,862 records from canine post-mortem, biopsy and cytology samples. The records were stored in the electronic patient record

system of the IVPZ. In 1987, when the digitized collection of data started, a punch card system was still used. There was no overlapping of data since dogs were only recorded in one system.

The ITP provided a set of diagnostic records (n = 20,674; 1983–2008) from canine post-mortem and biopsy samples and Zyto-Histo Diagnostics provided a set of diagnostic records (n = 3,530; 2007–2008) from canine biopsy samples. All samples from the IVPZ, ITP and Zyto-Histo Diagnostics were examined by histopathology.

Data Preparation

The datasets were compiled in a FileMaker database, which was exported into a Stata database (StataCorp LP, College Station, Texas, USA). Individual diagnostic records were standardized according to age, sex, neuter status and breed. The diagnoses were then coded according to the tumour topographical and morphological keys of the ICD-O-3 (Tables 1 and 2) and checked for plausibility using the original patient records. All tumour diagnoses were confirmed by histopathology. Epidermal cysts were excluded. Diagnoses were grouped for future comparison with human cancer and for this reason some of the groups may be unusual for veterinary pathologists. The groups are described in Table 3. The term 'epithelial tumour' is used in two different ways: firstly as an overall group including all types of epithelial tumours and secondly as a narrow group: 'epithelial* tumour' (Table 3).

Tumour groups included both malignant and benign tumours (i.e. adenoma and adenocarcinoma were categorized as one group 'adenoma, adenocarcinoma'). Each diagnostic record gave information about the tumour malignancy grade in an additional field. To investigate malignancy, each tumour group was divided into 'benign' (malignancy grade 0–2) and 'malignant' (malignancy grade 3–6) according to the ICD-O-3 classification. Because benign tumours can develop into malignant tumours of the same type, tumours such as adenoma and adenocarcinoma were not treated as separate groups. The same procedure was applied to related tumour groups; for example, lymphangioma and lymphangiosarcoma, osteoma and osteosarcoma, naevi and melanoma, myxoma and myxosarcoma. As different pathologists had worked on the samples, there were two different approaches to specifying the location of fibrosarcomas in subcutaneous tissue. Some pathologists used 'skin' as the location because skin biopsy was used to collect the sample, while others used 'soft tissue' to describe the origin of the tumours. We combined these two locations and recoded 'skin' as 'soft tissue' for fibrosarcomas.

Breed allocation was based on information in the diagnostic records. Mixed breed dogs were assigned according to the first-named breed or were classed non-specifically as crossbreed dogs. The 17 most common breeds, each comprising >900 individuals, were investigated further. The remaining breeds and records in which breed was recorded as 'unknown' were listed as 'other breeds'. The breed category 'shepherd' included German shepherd dogs, Beauceron Berger de Beauce, white shepherd dogs, Berger de Picardie, Berger de Savoie, Berger des Pyrénées, Groenendael, Laekenois, Malinois and Tervueren. Diagnostic records for dogs residing outside Switzerland were excluded from the analysis.

Table 1
Coding and grading of tumour diagnoses according to ICD-O-3

Diagnosis	*ICD-O code*
Odontogenic neoplasia	ICD-O 9270–9330
Trophoblastic tumours	ICD-O 9104
Epithelial tumour	ICD-O 8010–8587, ICD-O 9050–9058
Germ cell tumour	ICD-O 9060–9085
Lymphangioma, lymphangiosarcoma	ICD-O 9590–9960
Lymphoid tumour	ICD-O 9590–9960
Melanoma	ICD-O 8720–8730
Mesenchymal tumour	ICD-O 8680–8711, ICD-O 8800–9040, ICD-O 9120–9150, ICD-O 9580
Skeletal tumour	ICD-O 9180–9262
Neural tumour	ICD-O 9380–9570
Gonadal tumours	ICD-O 8610–8670
Unspecified tumours	ICD-O 8000

Table 2
Coding of tumour locations according to ICD-O-3

Location	*ICD-O C code*
Blood, haemopoietic system	ICD-O C 42
Neoplasia of bones, joints, cartilage	ICD-O C 40–41
Brain, meninges, other parts of CNS	ICD-O C 70–72
Mammary gland	ICD-O C 50
Endocrine gland	ICD-O C 73–75
Gastrointestinal tract	ICD-O C 16–26.8
Lymph nodes	ICD-O C 77
Male sexual organs	ICD-O C 60–63.2
Oral cavity, pharynx	ICD-O C 2.9–11
Other female sex organs	ICD-O C 51–58
Peripheral nerves, autonomic nervous system	ICD-O C 47
Respiratory system, intrathoracic organs	ICD-O C 30–39
Retroperitoneum, peritoneum	ICD-O C 48
Skin	ICD-O C 44
Soft tissues	ICD-O C 49
Urinary organs	ICD-O C 67–68

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Urinary organs	ICD-O C 67–68

Table 3
Example of tumour grouping for four selected groups

Diagnosis group	*Single diagnosis*	*Number*	*Percentage [%]*
Skeletal tumour ICD-O 9180–9262	Adamantinoma of long bones	103	8.7
	Chondroblastoma	22	1.86
	Chondroma, fibrochondrosarcoma	168	14.19
	Osteochondroma	11	0.93
	Osteofibroma	38	3.21
	Osteoma, osteosarcoma	842	71.11
Total of skeletal tumours		**1,184**	**100**
Gonadal tumours ICD-O	Granulosa cell tumour, granulosa cell carcinoma	93	8.72
8610–8670	Leydig cell tumour	450	42.17
	Luteoma	9	0.84
	Sertoli cell adenoma, Sertoli cell carcinoma	423	39.64
	Sertoli-Leydig cell tumour	92	8.62
Total of gonadal tumours		**1,067**	**100**
Gonadal germ cell tumour ICD-O	Embryonal carcinoma	3	0.45
9060–9085	Seminoma	632	95.47
	Teratoma	8	1.21
	Germ cell tumours	19	2.87
Total of germ cell tumours		**662**	**100**
Epithelial tumour ICD-O	Adenocarcinoma of anal glands	2,421	9.27
8010–8587, ICD-O 9050–9058	Adenocarcinoma with squamous metaplasia	190	0.73
	Adenoma, adenocarcinoma	12,348	47.27
	Adenomatous polyp, adenocarcinoma in adenomatous polyp	321	1.23
	Adrenal cortical adenoma, adrenal cortical adenocarinoma	168	0.64
	Basal cell carcinoma, adenoma	499	1.91
	Carcinoma, anaplastic type	296	1.13
	Cholangioma, cholangiocarcinoma	48	0.18
	Composite carcinoid	43	0.16
	Epithelial* tumour ICD-O 8010–9053	1,677	6.42
	Epithelioid mesothelioma	37	0.14
	Epithelioma	958	3.67
	Hepatoma, hepatocarcinoma	155	0.59
	Insulinoma	52	0.2
	Intracystic papillary adenoma, intracystic papillary adenocarcinoma	79	0.3
	Intraductal papilloma, intraductal papi	12	0.05
	Mesothelioma, biphasic, malignant	42	0.16
	Multifocal superficial basal cell carcinoma	231	0.88
	Papillary adenoma, adenocarcinoma	112	0.43
	Papillary carcinoma	871	3.33
	Pilomatrixoma	503	1.93
	Pulmonary adenomatosis, bronchiolo-alveolar adenocarcinoma	45	0.17
	Sebaceous adenoma, sebaceous adenocarcinoma	1,456	5.57
	Secretory carcinoma of the mammary gland	329	1.26
	Spindle cell carcinoma	72	0.28
	Squamous cell carcinoma	1,324	5.07
	Squamous papillomatosis	10	0.04
	Sweat gland adenoma, sweat gland adenocarcinoma	427	1.63
	Thymoma	96	0.37
	Transitional cell papilloma, transitional cell carcinoma	168	0.64
	Trichoepithelioma	1,132	4.33
Total of epithelial tumours		**26,122**	**100**

Results

Dataset

A total of 121,963 dogs were examined through histopathology, of which 63,214 (51.83%) were diagnosed with tumours. Of those, 59,124 (93.53%) had a single tumour and 4,090 (6.47%) had multiple tumours. A total of 35,232 (52.93%) of the tumours were benign and 31,336 (47.07%) were malignant. The proportion of tumour bearing patients versus patients without a tumour differed according to the method of examination: by biopsy histopathology 64.81% of the patients were diagnosed with a tumour, by cytological examination 41.96% and by post-mortem examination 31.04%.

[1] Table 3 was corrected. See corrigendum page 15.

Table 4
The 17 most common breeds out of a total of 183 breeds among 121,963 dogs

Breed	*Number*	*Percentage [%]*
Shepherd	12,354	10.13%
Crossbreed	12,193	10.00%
Retriever	11,429	9.37%
Swiss Mountain dog	7,774	6.37%
Poodle	7,214	5.91%
Dachshund	6,499	5.33%
Boxer	6,368	5.22%
Schnauzer	2,796	2.29%
Collie	2,206	1.81%
Yorkshire terrier	2,157	1.77%
Cocker spaniel	2,127	1.74%
Setter	2,105	1.73%
Great Dane	1,598	1.31%
Doberman pinscher	1,596	1.31%
Rottweiler	1,470	1.21%
West Highland white terrier	1,316	1.08%
Bulldog	1,016	0.83%
Parson Jack Russell terrier	981	0.80%
Other breeds (including dogs of unknown breed)	38,764	31.78%
Total of all breeds	121,963	100%

Breed Distribution

The dataset included 182 different dog breeds ($n = 101{,}281$). A large number of these were crossbreeds ($n = 12{,}193$) and some were of unclassified breed ($n = 8{,}489$). The most frequent breed was the Shepherd dog (10.13%), closely followed by crossbreeds (10.00%) and retrievers (9.37%) (Table 4).

Incidence Rates

Fig. 1 shows the influence of the examination methods on the annual tumour incidence rate. Post-mortem examination had a relatively stable annual incidence rate: 13 cases of neoplasia per 100,000 dogs in 1955 and 20 cases in 2008. A peak of 65 cases per 100,000 dogs was observed in the 1980s. Conversely, the overall annual tumour incidence rate rose from 13 cases of neoplasia per 100,000 dogs in 1955 to 695 cases in 2008. This trend is comparable with the rise in the incidence rate of biopsy and cytology cases, which increased from 141 cases of neoplasia per 100,000 dogs in 1968 to 675 cases in 2008.

Distribution of the Most Common Diagnoses

The most common tumours were epithelial (38.45%), mesenchymal (35.1%), lymphoid (13.23%), melanoma (3.90%), skeletal (1.74%) and gonadal tumours (1.57%). Fig. 2 presents a more detailed distribution of the diagnoses, with adenoma and adenocarcinoma (32.62%) at the top (see Fig. 3).

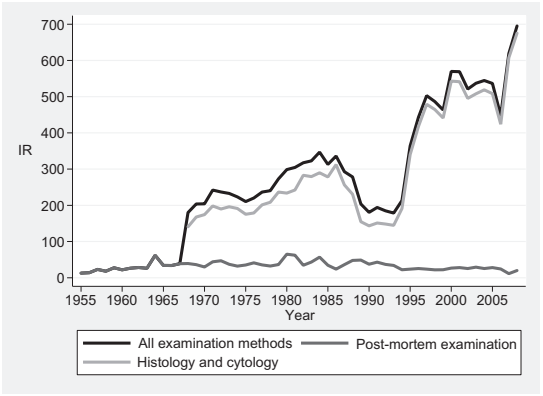

Fig. 1. The influence of examination methods on the annual tumour incidence rate (IR; i.e. number of tumours diagnosed per 100,000 dogs in the Swiss dog population).

The Most Prevalent Diagnoses over Time (1955–2008). The proportion of epithelial tumours declined from 45.65% in 1955 to 34.46% in 2008, while the proportions of mesenchymal and lymphoid tumours, melanoma and gonadal tumours rose. Mesenchymal tumours rose from 28.26% in 1955 to 34.36% in 2008, lymphoid tumours from 8.70% to 14.69%, melanoma from 0.00% to 5.18% and gonadal tumours from 0.00% to 2.47% (Fig. 2).

Malignancy of the Most Common Tumour Diagnoses. Of the total tumours, 47.07% were malignant. The following tumour groups had malignancy rates higher than the overall rate: skeletal tumours (96.61%), melanoma (87.21%), gonadal germ cell tumours (86.38%), epithelial tumours (56.52%) and lymphoid tumours (52.79%). The following tumour groups had malignancy rates lower than the overall

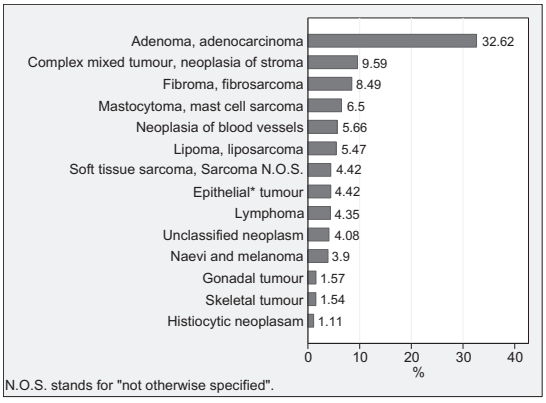

Fig. 2. Detailed most common tumour diagnoses (>1% of $n = 67{,}943$).

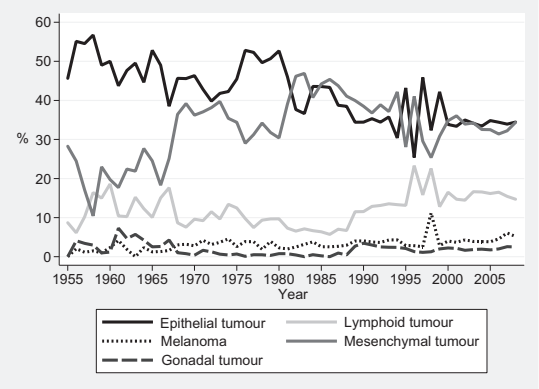

Fig. 3. The yearly most prevalent tumour diagnoses. The percentage of a tumour type among all tumour types diagnosed per year.

rate: neural tumours (43.38%), unclassified neoplasms (32.6%), mesenchymal tumours (29.65%), lymphangioma and lymphangiosarcoma (16.09%), gonadal tumours (8.15%) and odontogenic tumours (2.67%). Fig. 4 presents the malignancy rate of the most frequently occurring tumour groups.

A more accurate grouping shows that the following tumour groups had malignancy rates higher than the overall rate: mesothelial neoplasia (100%), complex epithelial neoplasia (99.47%), leukaemia (99.39%), transitional cell papilloma, transitional cell carcinoma (98.21%), other neoplasia of bones (96.45%), osteoma and osteosarcoma (95.49%), glial neoplasia (94.26%), epithelial* tumour (89.97%), soft tissue sarcoma (88.24%), naevi and melanoma (87.21%), gonadal germ cell tumour (86.38%), myxoma and myxosarcoma (83.24%), plasma cell neoplasia (82.44%), synovia-like neoplasia (53.49%), histiocytic neoplasia (52.13%), adenoma and adenocarcinoma (50.79%) and paraganglioma (48.5%).

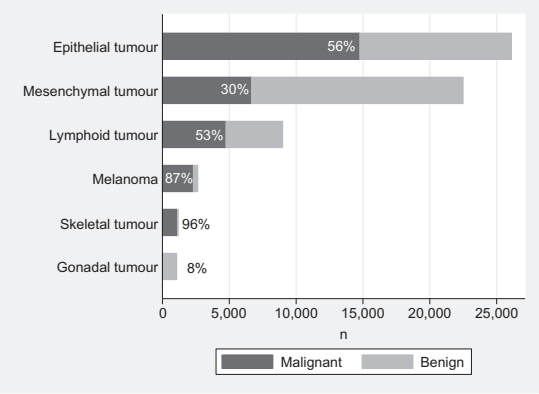

Fig. 4. Absolute (*n*) and relative (%) distribution of the malignancy in tumour diagnoses. In this figure, epithelial tumour includes ICD-O 8010–8587 and ICD-O 9050–9058.

Location of Tumours

Most of the tumours were located in the skin (32.29%), the mammary gland (20.53%) and the soft tissue (11.90%). Fig. 5 shows that the frequency of tumours in all other locations was below 10%. Due to the evaluation of all organs in post-mortem investigations, the distribution of locations of tumours is unbiased, as compared with biopsy and cytology samples (Fig. 6). The gastrointestinal tract (11.40%) and the respiratory system (10.63%) were the leading tumour locations. The largest variety of tumour types was found in the mouth and the pharynx, where seven different tumour types were identified (Fig. 7).

Age Distribution

The age distribution of the cases (Fig. 8) shows that most dogs, irrespective of tumour presence, were between 5 and 10 years of age (48.79%). Another large group consisted of dogs >10 years of age (21.42%). Only 16.80% of the dogs were between 1 and 5 years of age, and the group of dogs <1 year of age (6.84%) mainly consisted of animals without tumours (see Figs. 9 and 10).

Discussion

To our knowledge, the figures of 121,963 dogs and 67,943 tumour diagnoses collected over 53 years renders the Swiss Canine Cancer Registry the most comprehensive animal cancer registry at a national

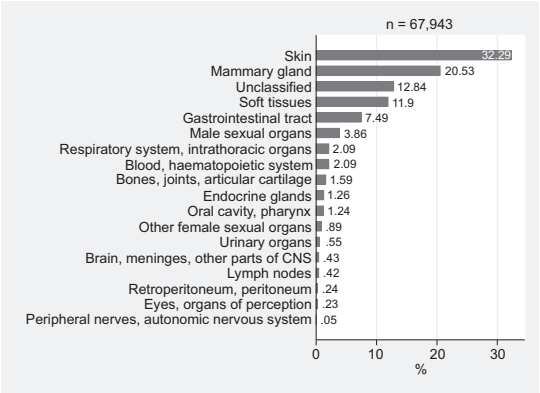

Fig. 5. Distribution of tumour locations diagnosed by all examination methods. *n*, number of all samples; %, proportion of tumour location.

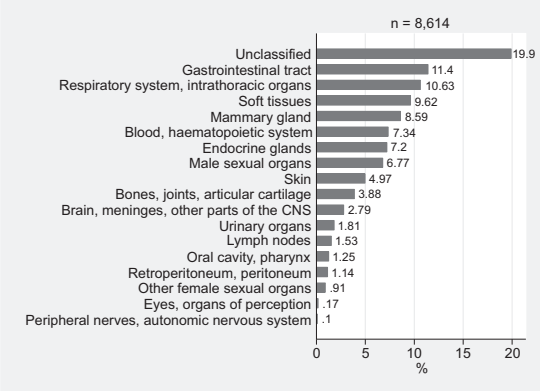

Fig. 6. Distribution of tumour locations diagnosed by post-mortem investigation. *n*, number of post-mortem samples; %, proportion of tumour location.

level. However, there are some shortcomings, which are typical of long-term retrospective studies. One such issue is that diagnoses were made by different pathologists at different time periods. The criteria for certain diagnoses may have changed over time and in some cases there may be a subjective factor in histopathological diagnostics. This problem was overcome by restricting data evaluation to those tumour entities that could be clearly identified and that have been known for a long time.

The yearly distribution of breeds in the Swiss Canine Cancer Registry reflects the change in breed fashion in the Swiss dog population (Pospischil *et al.*, 2013). In the 1950s and 1960s, poodles (13.80%), shepherds (12.66%), crossbreeds (10.61%), boxers (9.75%) and dachshunds (9.69%) were the most common breeds. From 1970 to 2008 the most common breeds were crossbreeds (10%), retrievers (9.97%), shepherds (9.87%) and Swiss Mountain dogs (6.53%).

During the study period, the Swiss dog population increased constantly and the relative tumour incidence rose dramatically, from 13 cases per 100,000 dogs at risk in 1955 to 695 in 2008. This trend could be explained by selection bias, due to the availability of new diagnostic methods, namely biopsy sampling (since 1968) and fine needle aspiration (since 1991). This trend may also have been influenced by a rising prevalence of tumours in dogs. In fact, similar to man, the life expectancy of dogs has risen continuously since 1955, due to advancements in veterinary medicine. An increased life expectancy, however, makes dogs more susceptible to tumours, since tumours tend to develop at an older age (Bonnett and Egenvall, 2010).

On the other hand, the tumour incidence rate in post-mortem samples did not increase over time. This might be explained partly by the decreasing relative number of post-mortem investigations, as dog owners increasingly tend to refuse a post-mortem examination. Moreover, since the introduction of biopsy sampling, tumours may have been diagnosed before death, so that a post-mortem investigation was no longer necessary.

Several additional factors may have contributed to the increasing canine tumour incidence rate in Switzerland. Firstly, the change in the role of dogs in society, from working dogs to family members, fully entitled to veterinary care, diagnostic examinations and therapeutic interventions. Secondly, the standard of living has generally risen over the years and dog owners can afford systematic diagnostic examinations. Thirdly, the density of licensed veterinary practices increased from two practices per 100,000 dogs to 346 practices per 100,000 dogs in Switzerland between 1955 and 2008 (personal information, Gesellschaft Schweizer Tierärztinnen und Tierärzte, the Swiss Society of Veterinarians). Fourthly, the evolution of environmental risk factors (e.g. UV radiation or air pollution) may have encouraged tumour development (Reif and Cohen, 1979; Porello *et al.*, 2006). Environmental factors responsible for dog tumours should be investigated in future research.

It is generally difficult to compare tumour incidences between animal cancer registries because of differences in the sampling methods (MacVean *et al.*, 1978; Brønden *et al.*, 2007, 2010; Vascellari *et al.*, 2009; Egenvall *et al.*, 2011). In order to estimate the population at risk, a telephone survey was undertaken in Northern Italy (Vascellari *et al.*, 2009). Data were collected from an animal health insurance company (Agria Ltd.) in Sweden (Egenvall *et al.*, 2011) or by counting the 'veterinarian-using' dogs in Tulsa, USA (MacVean *et al.*, 1978) and by legally regulated dog registration in Denmark in the Danish Dog Registry (Brønden *et al.*, 2010) and, since 2006, in Switzerland.

However, in Switzerland, the tumour incidence rate for 2008, which reached a value of 695 cases per 100,000 dogs, lies midway between the rates of other countries. For example, 282 cases per 100,000 dogs were observed in Northern Italy (Vascellari *et al.*, 2009), 500 cases per 100,000 dogs in Sweden (Egenvall *et al.*, 2005), 748 cases per 100,000 dogs in the UK (Dobson *et al.*, 2002) and 1,416 tumours per 100,000 dogs in Tulsa, USA (MacVean *et al.*, 1978). The observed malignancy distribution (47.07%) is similar to that of other cancer registries. It was reported as 38% by Brønden *et al.* (2010), 50% by

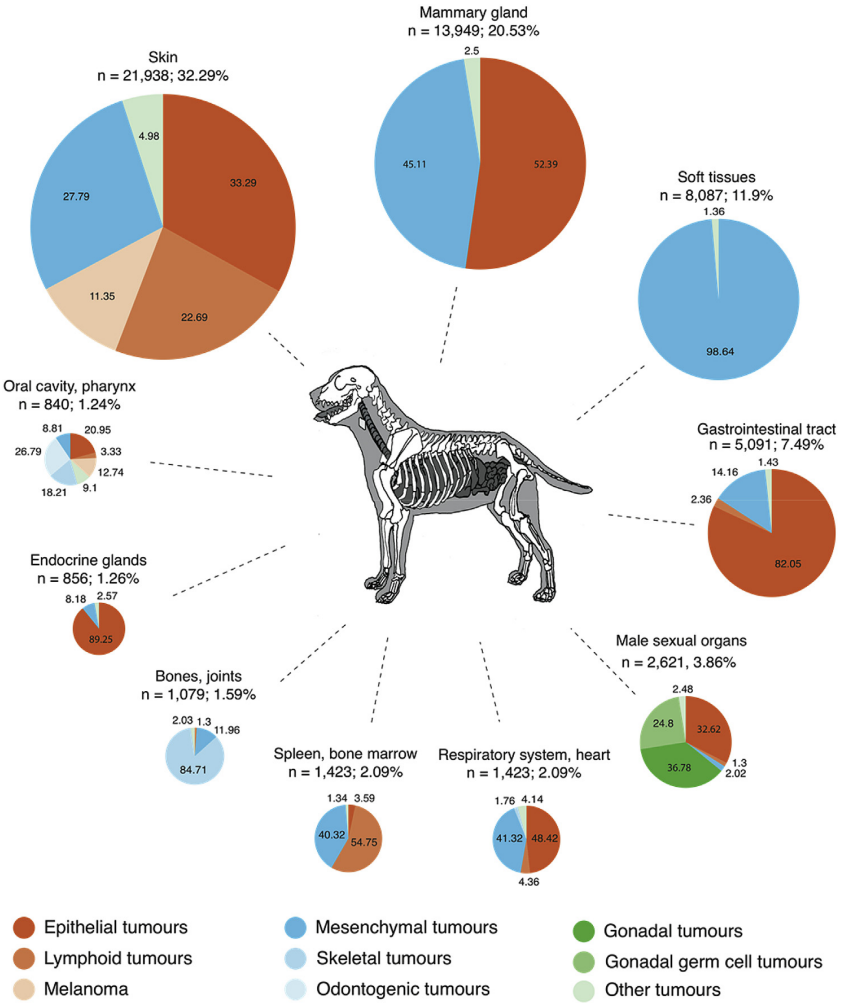

Fig. 7. Tumour location and diagnoses. *n*, number of tumours found in a location; %, proportion of the location compared with the total of locations. Figures in and around the slices show the relative proportion of tumour diagnoses/location. Tumour diagnoses <1% were added into 'other tumours'; locations <1% and unclassified locations were not listed. With the exception of 'male sexual organs', the listed locations are not sex specific.

Gamlem *et al.* (2008), 49% by Merlo *et al.* (2008) and 51% by Vascellari *et al.* (2009).

Skeletal tumours and melanomas showed the highest malignancy, with 96.61% and 87.21%, respectively. These figures are also similar to the results reported by Porello *et al.* (2006) and Ehrhart *et al.* (2013). Skin (32.29%), the mammary gland (20.53%) and soft tissues (11.90%) are the most frequent tumour locations, as confirmed by Dobberstein (1937), Mulligan (1949), Dorn (1967), MacVean *et al.* (1978), Bastianello (1983), Arnesen *et al.* (2001), Dobson *et al.* (2002), Gamlem *et al.* (2008), Vascellari *et al.* (2009) and Dobson (2013). These results are influenced by the fact that both locations are easy to access and to observe, both for the dog owner and the veterinarian.

The ranking of the tumour locations diagnosed in post-mortem investigations shows the highest values for the gastrointestinal tract (14.23%) and the respiratory system (10.63), including thoracic organs (13.28%). In the ranking of all tumours sampled through post-mortem and biopsy, the gastrointestinal tract (7.49%) and the respiratory system, including thoracic organs (2.09%), hold places 4 and 6, respectively, similar to the observations of Dobson *et al.* (2002), Porello *et al.* (2006), Vascellari *et al.* (2009)

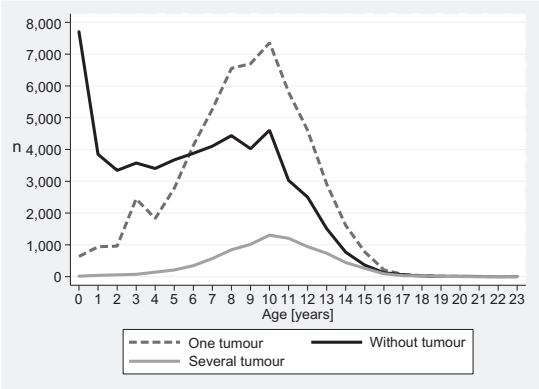

Fig. 8. Canine patients with none, one or several tumours per age. *n*, number of patients.

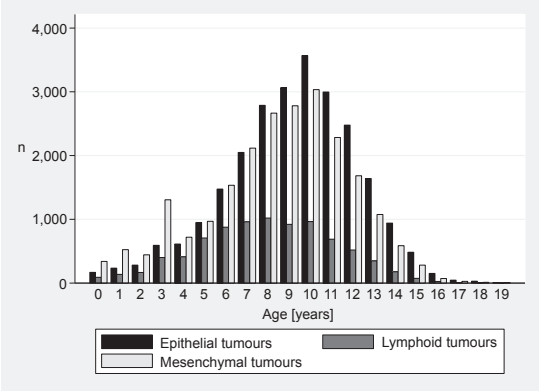

Fig. 9. Epithelial, mesenchymal and lymphoid tumours per age of patient. *n*, number of tumour types per age.

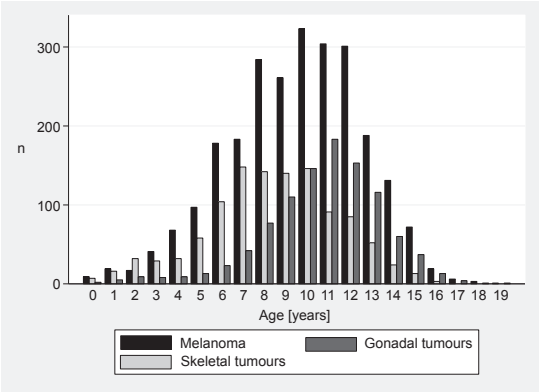

Fig. 10. Melanoma, gonadal neoplasia and skeletal tumours per age of patient. *n*, number of tumour types per age.

and Dobson (2013). The different frequencies in post-mortem samples and samples from biopsy suggest an over reporting of tumours at easily accessible locations, together with an underestimation of impenetrable locations.

The male sexual organs rank fifth (4.43%) in all examination methods and seventh (8.45%) in the post-mortem samples. Both results demonstrate that differences depend on the method of investigation and are similar to the findings of Dobberstein (1953), Mulligan (1949), Dorn (1967) and Bastianello (1983). Vascellari *et al.* (2009) observed that 13.4% of tumours were found in the male genital tract. In the Norwegian Canine Cancer Registry, tumours in the testes (2.4%) were less frequent than in the oral cavity (3.7%) (Gamlem *et al.*, 2008), which is an interesting difference in the distribution of these two tumour locations compared with those in the Swiss Canine Cancer Registry. Tumours of bones, joints and joint cartilage were similar in ranking for all examination methods and post-mortem investigations, with 1.82% and 4.84%, respectively. As previously mentioned, the investigation method had a strong impact on the distribution percentage. Gamlem *et al.* (2008) described tumours of bones, joints and joint cartilage as comparatively rare, with rates <1.00%. Oral tumours accounted for 1.24% of all tumours. Vascellari *et al.* (2009) found oral tumours more than twice as frequently in dogs in Northern Italy (2.6%) and Gamlem *et al.* (2008) found even more such tumours in dogs in Norway (3.7%). This discrepancy might be due to different sampling strategies. In the Swiss Canine Cancer Registry post-mortem data and biopsy samples were used, while in the Italian and Norwegian data, biopsy samples alone were used, where an overestimation of oral tumours might be expected. In accordance with the findings of Porello *et al.* (2006) and Thamm and Dow (2009), oral tumours represented the highest tumour type, including epithelial, lymphatic, mesenchymal, skeletal and odontogenic tumours and melanomas. Further research on these tumours may offer important insights for multimodality therapy in clinical investigations. For the development of new therapies it is advantageous that oral tumours develop rapidly and cannot be controlled by surgery alone (Porello *et al.*, 2006).

Adenoma and adenocarcinoma were the most frequent tumours in the Swiss Canine Cancer Registry, in concordance with the Tulsa Registry (MacVean *et al.*, 1978). In the Danish Veterinary Cancer Registry, the most frequently observed tumours were lipoma and adenoma (Brønden *et al.*, 2010). Another study reported histiocytoma, lipoma and adenoma as the most frequent tumours

(Dobson, 2013). The assigned tumour groups, however, are not always consistent, so comparison provides a rough overview only.

This study marks the beginning of a continuous registration of dog tumours in Switzerland, which will serve as reference for research in the fields of animal and human oncology. To be able to compare results of different registries in the future it is important that data collection is assimilated with other dog registries, as it is for human registries.

Acknowledgments

This study was financed through the financial support of the University of Zurich to A. Pospischil for acting as a fellow at the Collegium Helveticum during his fellowship period of 2009–2014. We thank Dr R. Dähler for his additional financial support and all colleagues of the Collegium Helveticum and the IVPZ, who contributed in various ways. We are grateful for the data from the veterinary pathology institutes, which made this and further studies possible. Finally, we thank H. Hofmann and H. Murray for revision of the English version.

Conflict of Interest Statement

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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CORRIGENDUM

Corrigendum to "The Swiss Canine Cancer Registry: A Retrospective Study on the Occurrence of Tumours in Dogs in Switzerland from 1955 to 2008" [J Comp Pathol 152 (2–3) (2015) 161–171]

K. Grüntzig[*], R. Graf[*], M. Hässig[†], M. Welle[‡], D. Meier[§], G. Lott[¶], D. Erni[#], N. S. Schenker[¶], F. Guscetti[¶], G. Boo[‖], K. Axhausen[††,*], S. Fabrikant[‖], G. Folkers[*] and A. Pospischil[¶,*]

[*] *Collegium Helveticum, Universität Zürich und Eidgenössische Technische Hochschule Zürich (ETHZ),* [†] *Departement Nutztiere Universität Zürich, Zürich,* [‡] *Institut für Tierpathologie Universität Bern, Bern,* [§] *Zyto-Histo Diagnostics, Freienstein,* [‖] *Geographisches Institut, Universität Zürich,* [¶] *Institut für Veterinärpathologie Universität Zürich, Zürich,* [#] *FocusedPublishing GmbH, CH-8332 Russikon and* [††] *Institut für Verkehrsplanung und Transportsysteme (IVT), ETHZ, Zürich, Switzerland*

The authors regret to say that a mistake has been found in the above paper.

The 2nd line of Table 3 is on page 164 states incorrectly, "Adamantinoma of long bones". The single diagnosis term should read "Adamantinoma of the jaw". Please find a correct version of Table 3 below:

Table 3
Example of tumour grouping for four selected groups

Diagnosis group	*Single diagnosis*	*Number*	*Percentage [%]*
Skeletal tumour ICD-O 9180–9262	Adamantinoma of the jaw	103	8.7
	Chondroblastoma	22	1.86
	Chondroma, fibrochondrosarcoma	168	14.19
	Osteochondroma	11	0.93
	Osteofibroma	38	3.21
	Osteoma, osteosarcoma	842	71.11

(*Continued*)

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Correspondence to: A. Pospischil (e-mail: apos@vetpath.uzh.ch).

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http://dx.doi.org/10.1016/j.jcpa.2015.04.008

Table 3 (*continued*)

Diagnosis group	*Single diagnosis*	*Number*	*Percentage [%]*
Total of skeletal tumours		**1,184**	**100**
Gonadal tumour ICD-O	Granulosa cell tumour, granulosa cell carcinoma	93	8.72
8610–8670	Leydig cell tumour	450	42.17
	Luteoma	9	0.84
	Sertoli cell adenoma, sertoli cell carcinoma	423	39.64
	Sertoli-Leydig cell tumour	92	8.62
Total of gonadal tumours		**1,067**	**100**
Gonadal germ cell	Embryonal carcinoma	3	0.45
tumour ICD-O	Seminoma	632	95.47
9060–9085	Teratoma	8	1.21
	Germ cell tumour	19	2.87
Total of gonadal germ cell tumours		**662**	**100**
Epithelial tumour ICD-O 8010–8587, ICD-O 9050–9058	Adenocarcinoma of anal glands	2,421	9.27
	Adenocarcinoma with squamous metaplasia	190	0.73
	Adenoma, adenocarcinoma	12,348	47.27
	Adenomatous polyp, adenocarcinoma in adenomatous polyp	321	1.23
	Adrenal cortical adenoma, adrenal cortical adenocarcinoma	168	0.64
	Basal cell carcinoma, adenoma	499	1.91
	Carcinoma, anaplastic type	296	1.13
	Cholangioma, cholangiocarcinoma	48	0.18
	Composite carcinoid	43	0.16
	Epithelial tumour ICD-O 8010–9053	1,677	6.42
	Epithelioid mesothelioma	37	0.14
	Epithelioma	958	3.67
	Hepatoma, hepatocarcinoma	155	0.59
	Insulinoma	52	0.2
	Intracystic papillary adenoma, intracystic papillary adenocarcinoma	79	0.3
	Intraductal papilloma, intraductal papillary carcinoma	12	0.05
	Mesothelioma, biphasic, malignant	42	0.16
	Multifocal superficial basal cell carcinoma	231	0.88
	Papillary adenoma, adenocarcinoma	112	0.43
	Papillary carcinoma	871	3.33
	Pilomatrixoma	503	1.93
	Pulmonary adenomatosis, bronchiolo-alveolar adenocarcinoma	45	0.17
	Sebaceous adenoma, sebaceous adenocarcinoma	1,456	5.57
	Secretory carcinoma of the mammary gland	329	1.26
	Spindle cell carcinoma	72	0.28
	Squamous cell carcinoma	1,324	5.07
	Squamous papillomatosis	10	0.04
	Sweat gland adenoma, sweat gland adenocarcinoma	427	1.63
	Thymoma	96	0.37
	Transitional cell papilloma, transitional cell carcinoma	168	0.64
	Trichoepithelioma	1,132	4.33
Total of epithelial tumours		**26,122**	**100**

This correction only applies to Table 3, the text of "Results" and "Discussion" is not affected. The authors apologize for this error.

Short Title: Analysis of the Swiss Canine Cancer Registry

Swiss Canine Cancer Registry 1955–2008: Occurrence of the Most Common Tumour Diagnoses and Influence of Age, Breed, Body Size, Sex and Neutering Status on Tumour Development

K. Grüntzig[*], R. Graf[*], G. Boo[*, §], F. Guscetti[†], M. Hässig[‡], K. W. Axhausen[*, ¶], S. Fabrikant[§], M. Welle[‖], D. Meier[#], G. Folkers[*] and A. Pospischil[*, †]

[*]Collegium Helveticum (Universität Zürich & ETHZ), Semper-Sternwarte, Schmelzbergstrasse 25, Zurich, [†]Institut für Veterinärpathologie and [‡]Departement Nutztiere, Vetsuisse-Fakultät Universität Zürich, Winterthurerstrasse 260, Zurich, [§]Geographisches Institut, Universität Zürich – Irchel, Winterthurerstrasse 190, Zurich, [¶]Institut für Verkehrsplanung und Transportsysteme (IVT), ETHZ, HIL F 31.3, Stefano-Franscini-Platz 5, Zurich, [‖]Institut für Tierpathologie, Vetsuisse-Fakultät Universität Bern, Länggassstrasse 122, Bern and [#]Zyto-Histo Diagnostik, Postfach 60, Rorbas-Freienstein, Switzerland.

Summary

This study is based on the Swiss Canine Cancer Registry, comprising 121,963 diagnostic records of dogs compiled between 1955 and 2008, in which 63,214 (51.83%) animals were diagnosed with tumour lesions through microscopical investigation. Adenoma/adenocarcinoma (*n* = 12,293, 18.09%) was the most frequent tumour diagnosis. Other common tumour diagnoses were: mast cell tumour (*n* = 4,415, 6.50%), lymphoma (*n* = 2,955, 4.35%), melanocytic tumours (*n* = 2,466, 3.63%), fibroma/fibrosarcoma (*n* = 2,309, 3.40%), haemangioma/haemangiosarcoma (*n* = 1,904, 2.80%), squamous cell carcinoma (*n* = 1,324, 1.95%) and osteoma/osteosarcoma (*n* = 842, 1.24%). The relative occurrence over time and the most common body locations of those tumour diagnoses is presented.

Analyses of the influence of age, breed, body size, sex and neutering status on tumour development were carried out using multiple logistic regression. In certain breeds/breed categories the odds ratios for particular tumours were outstandingly high: the boxer had higher odds ratios for mast cell tumour and haemangioma/haemangiosarcoma, as did the shepherd group for haemangioma/haemangiosarcoma, the schnauzer for squamous cell carcinoma and the rottweiler for osteoma/osteosarcoma. In small dogs, the risk of developing mammary tumours was three times higher than in large dogs. However, small dogs were less likely to be affected by many other tumour types (e.g. tumours of the skeletal system).

Examination of the influence of sex and neutering status on tumour prevalence showed that the results depend on the examination method. In all sampling groups the risk for female dogs of developing adenoma/adenocarcinoma was higher than for male dogs. Females had a lower risk of developing haemangioma/haemangiosarcoma and squamous cell carcinoma than males. Neutered animals were at higher risk of developing specific tumours outside the genital organs than intact animals.

The sample size allows detailed insight into the influences of age, breed, body size, sex and neutering status on canine tumour development. In many cases, the analysis confirms the findings of other authors. In some cases, the results are unique or contradict other studies, implying that further investigations are necessary.

Keywords: cancer registry; dog; statistical analyses; tumour

Introduction

To meet the challenge posed by the combination of potential aetiological factors in cancer, patient data and diagnoses need to be explored systematically (MacVean *et al.*, 1978; Brønden *et al.*, 2007, 2010; Vascellari *et al.*, 2009; Dobson, 2013; Waters *et al.*, 2014). This is the cornerstone of any epidemiological study of cancer that aims to investigate cancer development patterns in defined populations over time and space. The epidemiological study of cancer is therefore dependent on the availability of patient data that are usually stored in cancer registries.

In this context, the study of companion animal cancer registries is especially valuable. Firstly, companion animals and their owners share the same environment and are therefore mostly exposed to the same environmental cancer risk factors (Bukowski and Wartenberg, 1997; Backer *et al.*, 2001; Gamlem *et al.*, 2008; Marconato *et al.*, 2009; Bettini *et al.*, 2010). Secondly, similar genetic predisposing factors for cancer development have been found for man and animals (Jónasdóttir *et al.*, 2000; Patterson, 2000; Lingaas *et al.*, 2003; Breen, 2009; Pastor *et al.*, 2009; Phillips *et al.*, 2010; Ke *et al.*, 2011). For instance, canine renal cystadenocarcinoma and nodular dermatofibrosis (Jónasdóttir *et al.*, 2000; Lingaas *et al.*, 2003) and canine osteosarcoma (Phillips *et al.*, 2010) are well-known examples of syndromes linked to genetic conditions common to both dogs and man. The former complex was linked to a specific mutation also found in people affected by a similar syndrome; in the latter a linkage to a specific locus was found in both species. These findings underline the value of comparative studies in human and veterinary oncology as part of the 'One Health' concept (Breen, 2009).

The present study is based on the Swiss Canine Cancer Registry (Grüntzig *et al.*, 2015) and highlights the influences of age, breed, body size, sex and neutering status on the development of tumours in dogs. The size of the Swiss Canine Cancer Registry, which comprises 121,963 dogs and 67,943 tumour diagnoses, allows computation of meaningful statistics. To our knowledge, the Swiss Canine Cancer Registry is the most comprehensive animal cancer registry at a national level.

Materials and Methods

Data Source

The data originated from the Swiss Canine Cancer Registry (Grüntzig *et al.*, 2015) comprising 121,963 diagnostic records of dogs provided by three veterinary diagnostic laboratories in Switzerland: the Vetsuisse Faculty Institut für Veterinärpathologie, Zürich (IVPZ), the Vetsuisse Faculty Institut für Tierpathologie, Bern (ITPA) and the Zyto/Histo Diagnostik private veterinary diagnostic laboratory (based in Rorbas Freienstein). The data sets included diagnostic records from canine samples generated by three different examination methods: post-mortem analysis (and subsequent histopathological evaluation), biopsy sampling (with subsequent histopathological examination) and cytology. Biopsy and cytology samples are hereafter called ex-vivo samples. No cases were excluded; however, some parameters were missing due to incomplete reporting by the submitting veterinarians. All diagnoses in the Swiss Canine Cancer Registry were derived from a microscopical examination.

Data Preparation

In different time periods, different terms were used for the description of age, breed, sex and neutering status. Those differences were standardized by numerical coding. The diagnoses were then coded according to the tumour topographical and morphological keys of the ICD-O-3 (Fritz *et al.*, 2013) and checked for plausibility using the original patient records. All tumour diagnoses were based on either histopathological or cytological examination. Epidermal cysts were excluded.

The data included 215 castrated male dogs with tumours in the testes. Since it is common in those cases to castrate the patient while sampling the tumour, those dogs where re-classified as entire at the moment of tumour diagnosis.

Data sets missing the information on the sex and/or status of neutering of patients were excluded from the evaluation of the influence of these parameters on tumour development.

Breed allocation was based on information available in the diagnostic records, which was usually provided by the pet owner or by the submitting veterinarian. A declaration of one breed was accepted as reported, while a declaration comprising two breeds (in the case of an apparent mix with recognizable breeds) was categorized according to the breed mentioned first (i.e. a shepherd-cross was categorized under shepherd, a shepherd–boxer-cross likewise under shepherd, and a boxer–shepherd-cross under boxer). It was assumed that the breed mentioned first was the one more obvious from the external appearance. Therefore the breeds defined in this work cannot be considered pure breeds and a certain influence of mixed breeding must be acknowledged in the risk calculations. The proportion of manifestly non-pure breeds ranged between 0 and 18% in the breeds considered for analysis (Table 1). Because all such mixed breeds likely share at least 50% of their genetic information with the predominant breed, the content of non-breed related genome is maximally half in these animals. This should be taken into account while interpreting the results of the statistics. As an example, for the Swiss mountain dog, the breed with the highest proportion of manifestly crossed individuals (18.14%), the unrelated genome may theoretically account for a difference of 9% in the odds ratio.

A non-specific allocation such as mixed-breed, mongrel or crossbreed was categorized under crossbreed, since it was assumed that a phenotype typical for a known breed was lacking or not distinct.

The breeds/breed categories most frequently represented in the data set, each comprising at least 900 individuals, were retained for the analysis of risks related to breed (Table 1). In a preliminary investigation the breed ranking of the data set and the breed ranking of the Swiss dog population was compared in those years in which a reference population with known breed composition was available for use as a control (1963, 1999 and 2008) (Pospischil *et al.*, 2013). For those years the patient breed ranking correlated with that of the reference population, meaning that there was no significant difference in breed distribution between the Swiss dog population and the patient collective. The difference in the distribution of the individual breeds over time was controlled for year and proportional distribution.

The remaining breeds and the diagnostic records with unknown breeds were listed as ‘other breeds’. The breed category Swiss mountain dog includes Appenzeller mountain dogs, Bernese mountain dogs, Entlebucher mountain dogs, large Swiss mountain dogs, Swiss mountain dogs and mountain dogs. The breed category retriever includes Chesapeake Bay retriever, curly coated retriever, flat coated retriever, golden retriever, Labrador, Nova Scotia duck tolling retriever, retriever and sandriner (golden retriever crossed with Irish setter). The breed category setter includes English setter, Gordon setter, Irish red and white setter, Irish red setter, Irish setter and setter. The breed category shepherd includes German shepherd dog, Beauceron Berger de Beauce, white shepherd, Berger de Picardie, Berger de Savoie, Berger des Pyrénées, Groenendael, Laekenois, Malinois and Tervueren.

For the examination of the influence of body size on tumour development two groups were established. ‘Large breeds’ comprised the doberman, great Dane, retriever, rottweiler, Swiss mountain dogs, shepherd and setter. ‘Small breeds’ comprised the bulldog, dachshund, Parson Jack Russell, West Highland white terrier and Yorkshire terrier.

Statistical Evaluation

Data editing and statistical analyses were performed using Stata Software (Stata Corp., 2011; Stata Statistical Software: Release 12; College Station, Texas, USA). Statistical analyses were carried out using a Chi-Square/Fisher’s exact test. Significant univariable variables were further integrated in a multiple logistic regression model using binary logistic models and stepwise backward procedure. The following variables were included in the model as fixed terms: sex, neutering status, breed, age, year, method of examination and canton of origin. The first four variables are random variables related to the animals and were also used for the specific evaluations on cancer frequency. The three latter variables were random factors related to time,

examination method and spatial distribution. The underlying Stata model for the multiple logistic regression was <logistic vary varx1 varx2 varx3 varx4 varx5 varx6 varx7>, whereby vary = tumour, varx1 = sex, varx2 = neutering status, varx3 = breed, varx4= age, varx5= year of examination, varx6= method of examination, varx7= canton of origin. $P < 0.05$ was considered to be significant and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. The power was set at 0.8. In the statistical evaluation, crossbreeds were used as the standard for comparisons with the remaining breeds, since they were assumed to have the largest genetic variation. For the evaluation of influence of sex and neutering status (Fig. 6) on overall tumour development, the data were divided into two subsets based on the examination method: post-mortem samples and ex-vivo samples. The results of the following three groups were compared: post-mortem samples, ex-vivo samples and all samples. For the evaluation of the influence of sex and neutering status on most common tumour diagnoses and locations (Tables 2–4), the total data set (all samples) was compared with the post-mortem sample data subset. The analyses of the influence of age on specific tumour development was biased by the low number of cases aged >15 years. Therefore results are shown until the age of 15.

Results

The Swiss Canine Cancer Registry consists of records from 126,693 dogs that underwent pathological examination. The number of patients with confirmed tumours was 63,214 (51.83%). Some dogs were diagnosed with multiple primary tumours, adding up to a total of 67,943 diagnosed tumour lesions.

The age distribution has been previously presented (Grüntzig *et al.*, 2015). A large number of the dogs were crossbred (*n* = 12,193; 10.00%). Breed distribution is given in Table 1. The collective comprised 56,062 (45.97%) male dogs and 61,754 (50.63%) female dogs. The neutering status was recorded as entire in 59,902 (49.11%) dogs, neutered in 26,127 (21.42%) dogs (8,845 male, 17,731 female) and not specified in 35,934 (29.46%) dogs.

The following results show the influence of breed on the most common tumour types, as well as of age, body size, sex and neutering status on the overall and specific tumour occurrence. In addition, the influence of sex and neutering status on the anatomical locations is reported. Their occurrence patterns over the years are also included. The classification and distribution of the tumour species of the data set is presented in Supplementary Table 1.

Table 1 Frequencies of the 17 most common breeds/breed categories in the registry and their relative proportions of crossbreeds and ensuing proportion of unrelated genome.

Breed/breed category	Total number*		Thereof manifestly crossed		Unrelated genome
Shepherd	12,354	(10.13%)	867	(7.02%)	3.51%
Crossbreed	12,193	(10.00%)	12,193	(100%)	n.s.
Retriever	11,429	(9.37%)	802	(7.02%)	3.51%
Swiss Mountain Dog	7,774	(6.37%)	1,410	(18.14%)	9.07%
Poodle	7,214	(5.91%)	173	(2.40%)	1.20%
Dachshund	6,499	(5.33%)	189	(2.91%)	1.46%
Boxer	6,368	(5.22%)	127	(1.99%)	0.99%
Schnauzer	2,796	(2.29%)	156	(5.58%)	2.79%
Collie	2,206	(1.81%)	223	(10.11%)	5.06%
Yorkshire Terrier	2,157	(1.77%)	7	(0.32%)	0.16%
Cocker Spaniel	2,127	(1.74%)	19	(0.89%)	0.45%
Setter	2,105	(1.73%)	105	(4.99%)	2.49%
Great Dane	1,598	(1.31%)	44	(2.75%)	1.38%

Doberman Pinscher	1,596	(1.31%)	72	(4.51%)	2.26%
Rottweiler	1,470	(1.21%)	63	(4.29%)	2.15%
West Highland White Terrier	1,316	(1.08%)	3	(0.23%)	0.12%
Bulldog	1,016	(0.83%)	0	(0.00%)	0.00%
Parson Jack Russell Terrier	981	(0.80%)	75	(7.65%)	3.83%
Other breeds (including dogs of unknown breeds)	38,764	(31.78%)	n.s.	n.s.	n.s.
Total of all breeds	121,963	(100%)	16,528	(13.55%)	7.78%

* Dogs were allocated to a certain breed based on the owner's claims; crossbreeds with dominant traits of a breed were included
n.s.: not specified

Adenoma/Adenocarcinoma (ICD –O 8140)
Adenomas/adenocarcinomas (*n* = 12,293, 18.09%) were the most common tumour diagnosed overall. From 1955 to 1985, approximately 30 to 40% of the diagnosed tumours were adenomas/adenocarcinomas. After 1985, the frequency of these diagnoses progressively dropped to 12% in 2008 (Fig. 1). Adenomas/adenocarcinomas were most commonly diagnosed in the mammary gland (*n* = 6,805; 55.36%) and in the gastrointestinal tract (*n* = 1,020; 8.30%). Using multiple regression analysis, the odds ratios of the dog breeds/breed categories developing an adenoma/adenocarcinoma were compared with those of the crossbreds (OR = 1). The Yorkshire terrier, the poodle, the cocker spaniel, the collie, the dachshund and the West Highland white terrier presented with significantly higher odds ratios in comparison with Crossbreds and the other breeds/breed categories included in the analysis. Breeds/breed categories with lower odds ratios were the rottweiler, the great Dane, the bulldog, the retriever, the doberman, the schnauzer, the Swiss mountain dog, the setter, the boxer and the shepherd (Fig. 2).

Mast Cell Tumours (ICD-O 9740)
Among the 67,943 neoplasms, 4,415 (6.50%) were diagnosed as a mast cell tumour. Between 1955 and 2008 the relative frequency of mast cell tumours rose with considerable fluctuations from 2.1% to 8.4% of the overall tumour diagnoses (Fig. 1). Mast cell tumours (*n* = 4,415) were mainly diagnosed in the skin (*n* = 4,324; 97.94%). The boxer showed outstanding significantly higher odds ratios of developing a mast cell tumour in comparison with crossbreds and to the other breeds/breed categories. Other breeds with higher risk were the Swiss mountain dogs, the retriever and the bulldog. Breeds/breed categories with lower odds ratios were the collie, the rottweiler, the West Highland white terrier, the shepherd, the poodle, the Yorkshire terrier, the cocker spaniel, the doberman and the dachshund (Fig. 2).

Lymphoma (ICD-O 9590, 9591, 9700)
Among the 67,943 diagnosed tumours, 2,955 (4.35%) were lymphomas. Between 1955 and 2008 the relative frequency of lymphoma decreased from 6.52% to 3.97% per year and from 1968 to 1988 it was around 2% (Fig. 1). Lymphomas (*n* = 2,955) were most commonly diagnosed in the lymph nodes (*n* = 1,362; 46.09%) and in unspecified locations (*n* = 425; 14.38%), followed by the blood and haemopoietic system (*n* = 380; 12.86%), skin (*n* = 234; 7.92%), the spleen (*n* = 206;

6.97%) and the liver (*n* = 69; 2.34%). Logistic regression revealed that the rottweiler has a markedly higher odds ratio of developing a lymphoma than crossbreds and other breeds/breed categories included in the analysis. Another breed category with higher odds ratios was the Swiss mountain dog. The poodle, the Yorkshire terrier, the dachshund, the retriever and the shepherd had lower odds ratios for lymphoma (Fig. 2).

Melanocytic Tumours (ICD-O 8720, 8730)
Among the 67,943 neoplasms diagnosed, 2,466 (3.63%) were melanocytic tumours. From 1955 to 2008 the relative frequency of melanocytic tumours rose from under 2% to over 4% (Fig. 1). The most common anatomical locations for melanocytic tumours (*n* = 2,466) were the skin (*n* = 2,309; 93.6%) and the oral cavity/nasopharynx (*n* = 106; 4.3%). Multiple regression analysis revealed that the odds ratios for the following dog breeds/breed categories of developing a melanocytic tumour were higher than those of crossbreds and the other breeds/breed categories included in the analysis: the setter, the schnauzer, the rottweiler, the retriever, the poodle, the doberman, the dachshund and the cocker spaniel. The bulldog, the West Highland white terrier, the collie, the boxer and the Great Dane presented with lower odds ratios for melanocytic tumours (Fig. 2).

Fibroma/Fibrosarcoma (ICD-O 8810, 8812)
Among the 67,943 tumours, 2,309 (3.40%) were diagnosed as a fibroma/fibrosarcoma. Between 1960 and 1996 the relative frequency of fibroma/fibrosarcoma increased with several fluctuations from 1.16% to 6.71% of the total tumour number. From 1996 to 2008 their relative frequency was between 2.10% and 3.56%. (Fig. 1). The most common anatomical locations for fibroma/fibrosarcoma (*n* = 2,309) were the soft tissues (*n* = 1,080; 46.77%) and the skin (*n* = 1,040; 45.04%). The setter, the Swiss mountain dog, the rottweiler, the retriever, the doberman and the boxer had higher odds ratios of developing fibroma/fibrosarcoma than did crossbreds and the other breeds/breed categories included in the analysis. The West Highland white terrier, the Yorkshire terrier, the dachshund and the poodle presented with lower odds ratios for fibroma/fibrosarcoma (Fig. 2).

Haemangioma/Haemangiosarcoma (ICD-O 9120, 9121)
Among the 67,943 diagnosed tumours, 1,904 (2.80%) were a haemangioma/haemangiosarcoma. Between 1955 and 2008 the relative frequency of these tumours rose from 0 to 3.45%, reaching a peak of 7.92% in 1996 (Fig. 1). The most common anatomical locations for haemangioma/haemangiosarcoma (*n* = 1,904) were soft tissues (*n* = 1,203, 63.18%) and the skin (*n* = 459; 24.11%), followed by the blood/haemopoietic system (*n* = 113; 5.93%). The shepherd (OR 1.806 [CI = 1.518, 2.150]) and the boxer (OR 1.850 [CI = 1.506, 2.261]) showed higher odds ratios of developing a haemangioma/haemangiosarcoma than crossbreds and the other breeds/breed categories included in the analysis. The West Highland white terrier, the Yorkshire terrier, the rottweiler, the poodle, the doberman, the great Dane, the cocker spaniel, the bulldog, and the dachshund presented with lower odds ratios for haemangioma/haemangiosarcoma (Fig. 2).

Squamous Cell Carcinoma (ICD-O 8070, 8071, 8078)
Among the 67,943 tumours, 1,324 (1.95%) were diagnosed as a squamous cell carcinoma. After a peak of 7.46% in 1958 the relative frequency of squamous cell carcinoma fluctuated between 0.94% and 4.02% of the overall tumour diagnoses until 1999. From 2000 to 2008 it was between 1.47% and 2.29% (Fig. 1). The high numbers in the 1950s might result from a bias due to the low amount of tumour data available from this period. The most common anatomical locations for squamous cell carcinoma (*n* = 1,324) were unspecified locations (*n* = 615; 46.5%), the skin (*n* = 601; 45.4%) and the oral cavity/nasopharynx (*n* = 56; 4.23%). Here, results for the schnauzer revealed a seven-fold higher risk (OR 7.712 [CI = 6.031, 9.860]) of developing a squamous cell carcinoma than the other breeds/breed categories included in the analysis. The boxer presented with a lower odds ratio for squamous cell carcinoma (Fig. 2).

Osteoma/Osteosarcoma (ICD-O 9180)

Among the 67,943 tumours, 842 (1.24%) were diagnosed as an osteoma/osteosarcoma. From 1955 to the late 1960s the relative frequency of osteoma/osteosarcoma was variable, ranging between 6% and 0% of the overall tumour diagnoses. In the 1970s and 1980s it was constantly under 1%. Up to 2008 it rose to 1.56%, with two peaks over 2% in the 1990s (Fig. 1). The most common anatomical locations for osteoma/osteosarcoma were bones and joints (n = 746; 88.60%), followed by skin (n = 26; 3.08%). The rottweiler (OR 3.321 [CI = 2.321, 4.752]) and the great Dane (OR 1.936 [CI = 1.248, 3.003]) presented with a higher risk of developing an osteoma/osteosarcoma than crossbreds and the other breeds/breed categories included in the analysis. The bulldog, the dachshund, the West Highland white terrier, the Parson Jack Russell terrier, the Yorkshire terrier, the poodle, the cocker spaniel and the schnauzer presented with lower odds ratios for osteoma/osteosarcoma (Fig. 2).

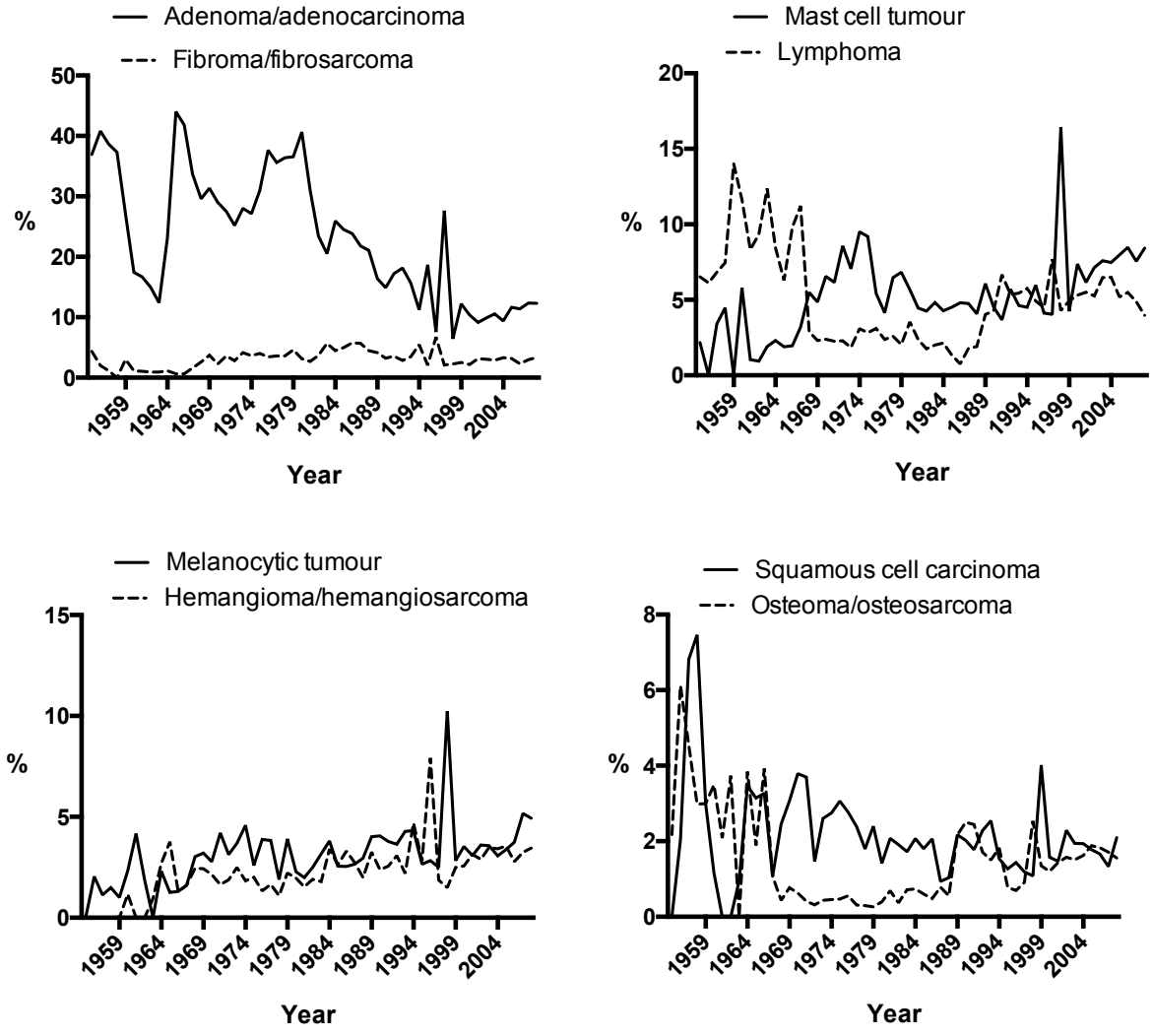

Fig. 1. Relative tumour frequencies between 1955 and 2008.

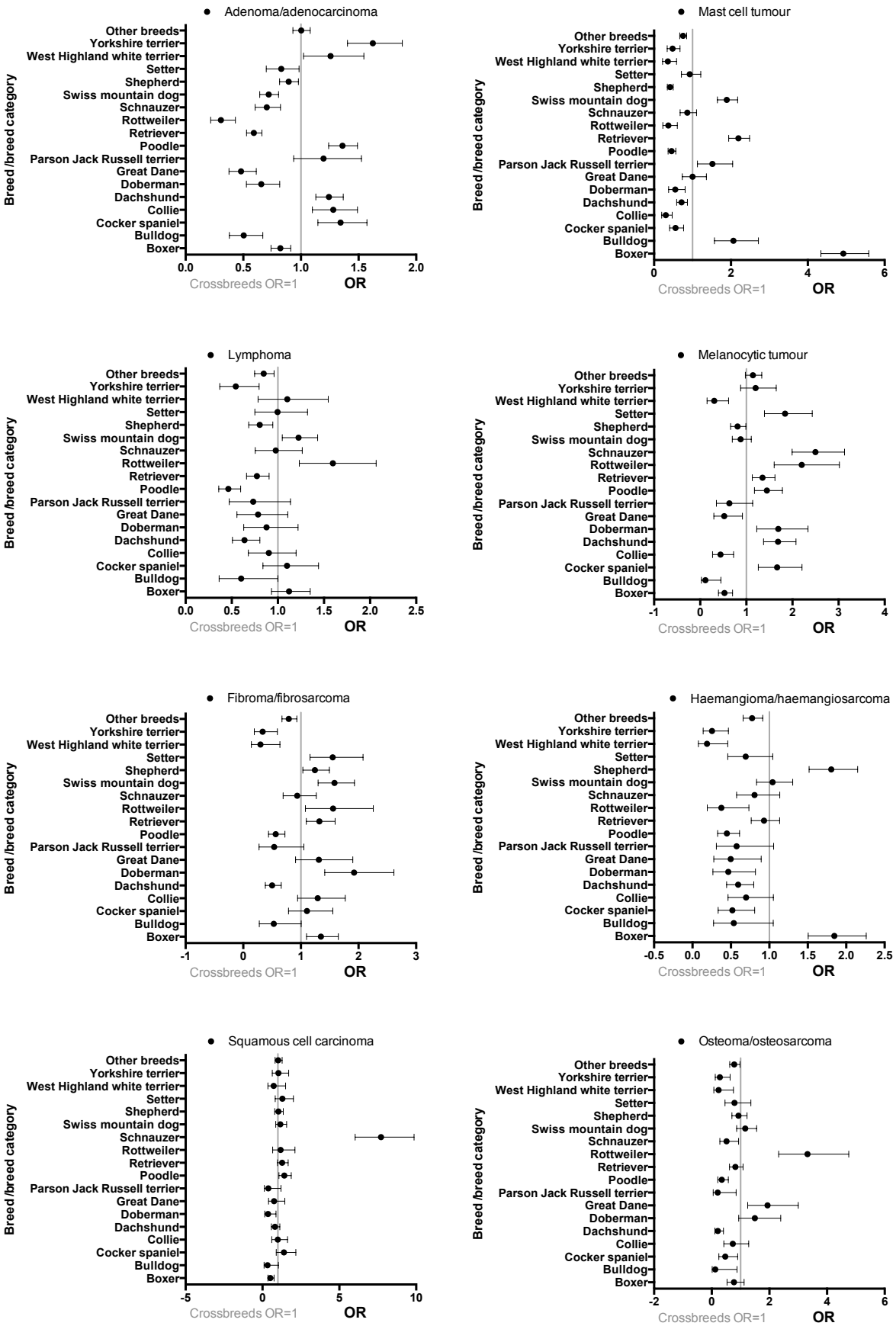

Fig. 2. Odds ratios (ORs) and 95% confidence intervals (CIs) for the most common dog breeds/breed categories of developing specific tumours compared with those for crossbreds (OR = 1). The number of observations was 126,692.

Influence of Age on Overall Tumour Development

Analyses of the influence of age revealed that the risk of developing adenoma/adenocarcinoma, melanocytic tumours and squamous cell carcinoma increased almost constantly with age. The risk of developing mast cell tumours, fibroma/fibrosarcoma, haemangioma/haemangiosarcoma and osteoma/osteosarcoma was only moderately influenced by increasing age after the age of 3, 4, 5 and 6 years, respectively. The risk of developing a lymphoma increased constantly with age until 6 years and decreased thereafter (Figs. 3, 4).

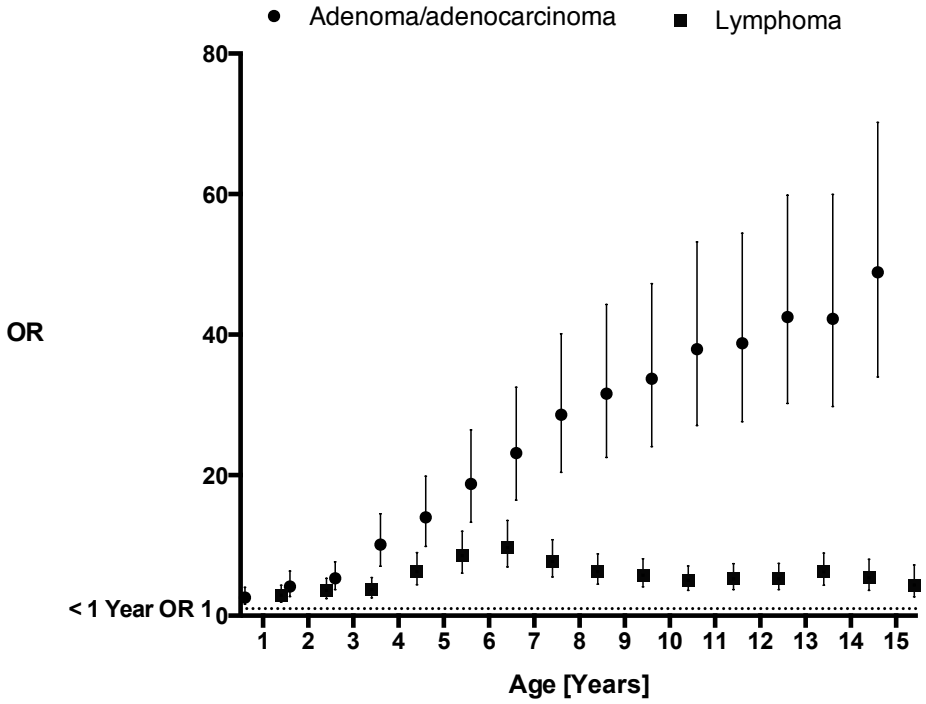

Fig. 3. Odds ratios (ORs) and 95% confidence intervals (CIs) for patients at different ages of developing different tumour types compared with patients aged <1 year (OR = 1). The number of observations was: 126,692 for adenoma/adenocarcinoma and 126,665 for lymphoma.

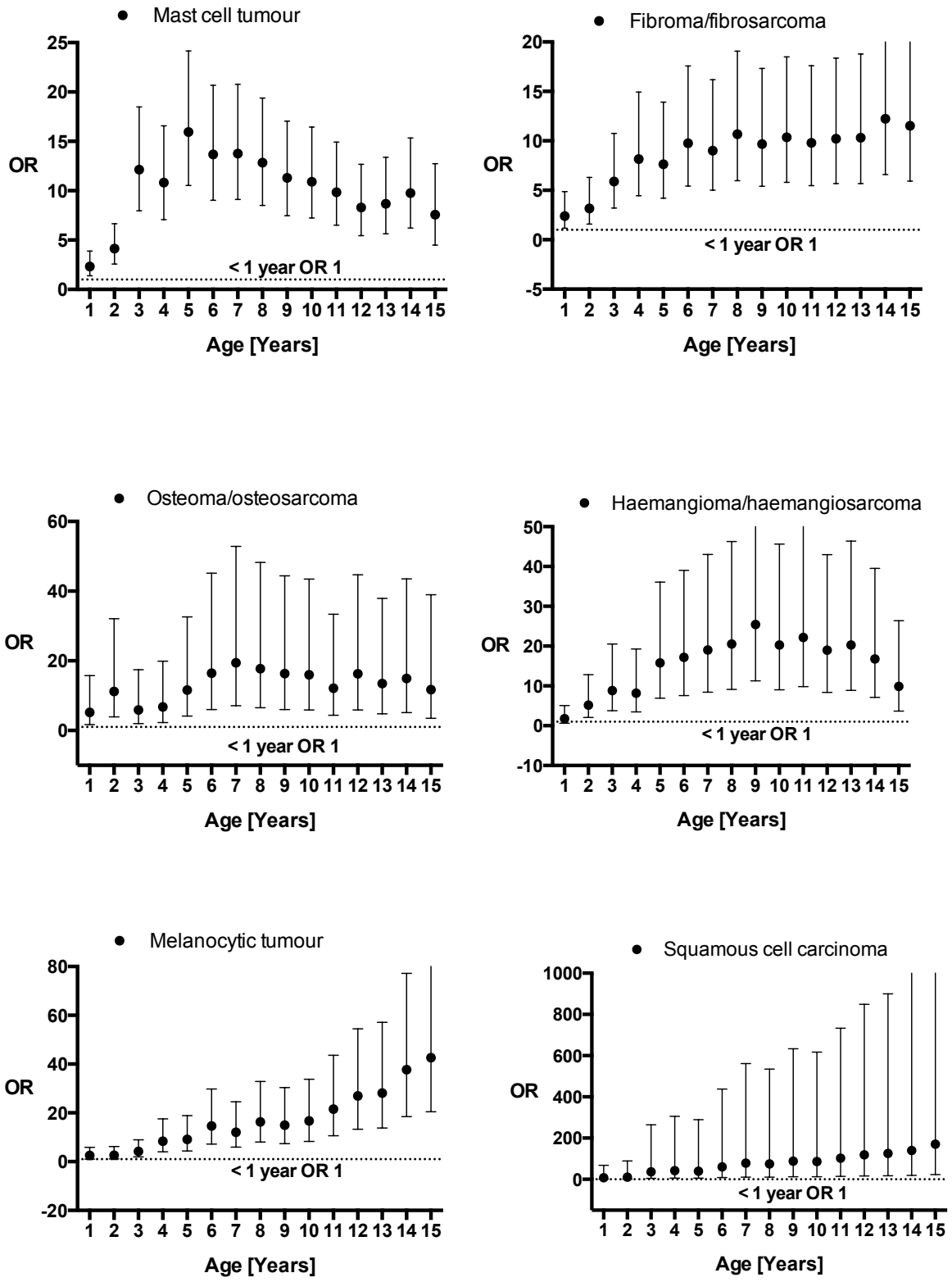

Fig. 4. Odds ratios (ORs) and 95% confidence intervals (CIs) for patients at different ages of developing different tumour types compared with patients aged <1 year (OR = 1). The number of observations was: 126,682 for mast cell tumour, 126,665 for fibroma/fibrosarcoma, 126,411 for osteoma/osteosarcoma; 126,593 for haemangioma/haemangiosarcoma; 126,651 for melanocytic tumours and 126,665 for squamous cell carcinoma.

Influence of Breed on Overall Tumour Development

Boxer (OR 1.700 [CI = 1.592, 1.815]), cocker spaniel (OR 1.504 [CI = 1.365, 1.658]), poodle (OR 1.443 [CI = 1.354, 1.537]), Swiss mountain dog (OR 1.357 [CI = 1.278, 1.440]), dachshund

(OR 1.305 [CI = 1.223, 1.392]), setter (OR 1.299 [CI = 1.179, 1.431]), schnauzer (OR 1.289 [CI = 1.182, 1.405]) and retriever (OR 1.278 [CI = 1.211, 1.348]) were at higher risk of developing a tumour than were crossbreds. Great Dane (OR 0.532 [CI = 0.475, 0.596]), bulldog (OR 0.615 [CI = 0.537, 0.704]), West Highland white terrier (OR 0.701 [CI = 0.622, 0.789]), Parson Jack Russell terrier (OR 0.791 [CI = 0.690, 0.906]), rottweiler (OR 0.829 [CI = 0.739, 0.929]), doberman (OR 0.833 [CI = 0.747, 0.929]), collie (OR 0.840 [CI = 0.764, 0.923]), shepherd (OR 0.872 [CI = 0.827, 0.919]) and Yorkshire terrier (OR 0.897 [CI = 0.816, 0.986]) were at lower risk of developing a tumour than crossbreds (Fig. 5). There was no generally higher risk for defined breeds/breed categories as a whole group compared with mixed breeds.

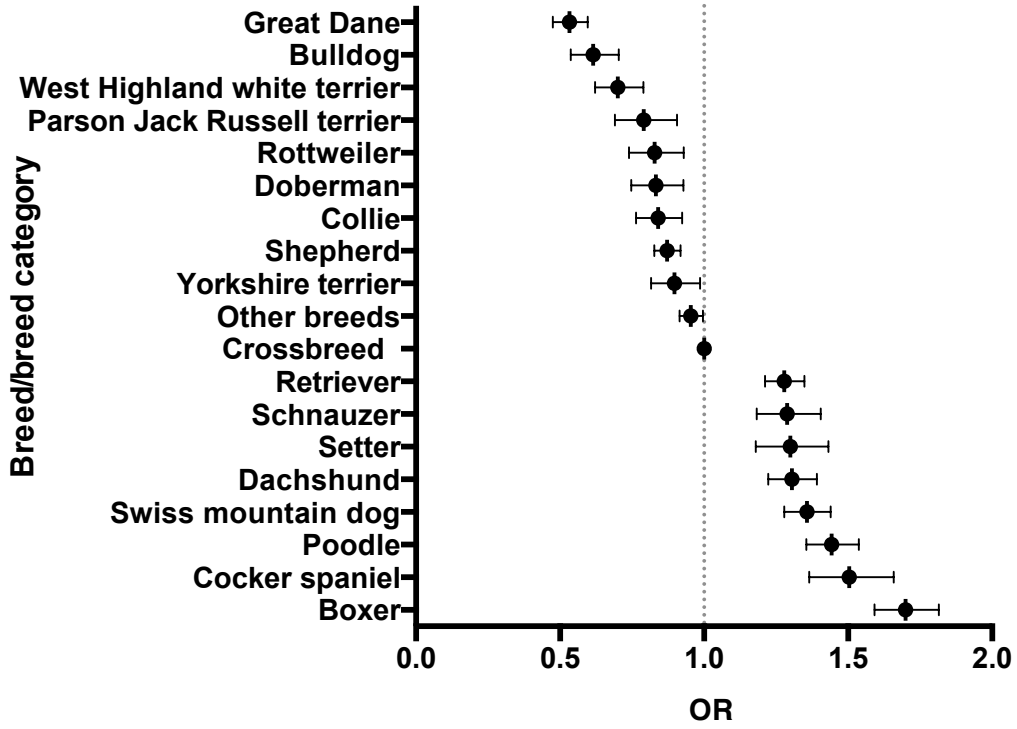

Fig. 5. Odds ratio (OR) for defined breeds/breed categories of developing a tumour compared with crossbreds. The number of observations was 126,692.

Influence of Body Size on Overall Tumour Development

There was no general difference in the risk of developing a tumour for either body size group. However, the small breed group was three times more frequently affected by tumours of the mammary glands (OR 3.034 [CI = 2.834, 3.256]) and had a 54.82% higher risk of developing a tumour of the endocrine glands (OR 1.548 [CI = 1.190, 2.014]) than the large breed group. Small breeds were at less risk of developing tumours in the following locations: soft tissues (OR 0.402 [CI = 0.361, 0.448]), skin (OR 0.819 [CI = 0.774, 0.868]), retroperitoneum and peritoneum (OR 0.308 [CI = 0.141, 0.672]), respiratory system and intrathoracic organs (OR 0.430 [CI = 0.264, 0.439]), other female sexual organs (OR 0.274 [CI = 0.184, 0.408]), bones, joints and articular cartilage (OR 0.192 [CI = 0.131, 0.282]).

Influence of Sex and Neutering Status on Overall Tumour Development

A closer look at the influence of sex and neutering status on overall tumour prevalence showed that the results depend on the examination method (Fig. 6). In post-mortem samples, tumour risk was 81.64% higher (OR 1.816 [CI = 1.570, 2.101]) for neutered males than for entire males (by definition OR = 1.000). Tumour risk was two times higher (OR 2.070 [CI = 1.831, 2.340]) for neutered females than for entire females. In ex-vivo samples, tumour risk was only 6.18% higher (OR 1.062 [CI = 1.010, 1.117]) for neutered males than for entire males. Tumour risk was

14.20% lower (OR 0.858 [CI = 0.823, 0.894]) for neutered females than for entire females (Fig. 6).

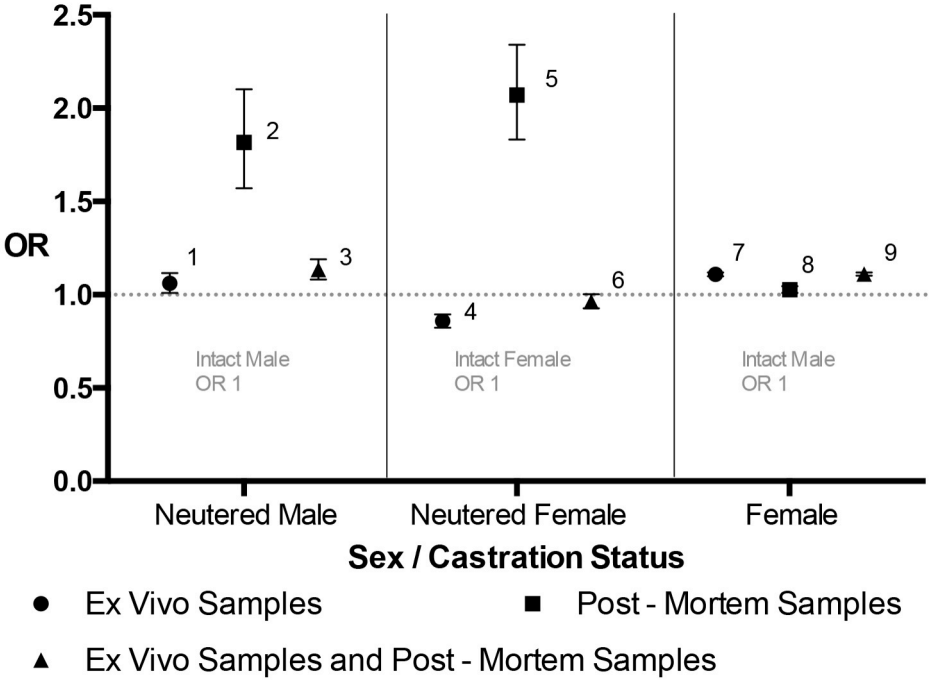

Fig. 6. Odds ratios (OR) of developing a tumour by sex and castration status, subclassified by examination method. The number of observations was: [1] 35,649; [2] 7,357; [3] 43,006; [4] 40,243; [5] 6,144; [6] 46,387; [7] 95,746; [8] 26,733; [9] 122,479.

Influence of Sex and Neutering Status on Specific Tumour Development

Hereafter, only results significant in both investigated groups (i.e. the total data set and the subset of post-mortem samples) are reported. All results are presented in Tables 2–5. The distribution of tumour locations for the investigated groups is presented in Supplementary Tables 2–5.

The odds ratios for female dogs of developing an adenoma/adenocarcinoma were significantly higher than those for male dogs. Females presented with lower odds ratios for haemangioma/haemangiosarcoma and squamous cell carcinoma than males (Table 2).

Neutered male dogs presented with higher odds ratios of developing the following tumours than entire male dogs: adenoma/adenocarcinoma, lymphoma, mast cell tumour and osteoma/osteosarcoma (Table 3).

Neutered female dogs had lower odds ratios of developing adenoma/adenocarcinoma than entire females. Neutered female dogs presented with higher odds ratios for the following tumours: haemangioma/haemangiosarcoma, lymphoma, mast cell tumour and melanocytic tumour (Table 3).

Influence of Sex and Neutering Status on Tumour Location

Female dogs presented with higher odds ratios of developing mammary gland tumours than male dogs (Table 4).

Neutered male dogs presented with higher odds ratios for skin tumours, tumours of the blood and the hemopoietic system, tumours of the endocrine glands, the respiratory system and intrathoracic organs and unspecified locations than entire male dogs (Table 5).

Neutered female dogs presented with higher odds ratios for skin and soft tissue tumours, tumours of the blood and the hemopoietic system, the gastrointestinal tract, the oral cavity and pharynx, the respiratory system and intrathoracic organs and the urinary organs than entire female dogs. They had lower odds ratios for tumours of the mammary gland (Table 5).

To verify the results above, the investigations for neutered females versus entire females were repeated, excluding tumours of the mammary gland. The deviations from the results that included mammary gland tumours were negligible (Supplementary Tables 6–7). An exception was the result for adenoma/adenocarcinoma in post-mortem samples: neutered females had a higher risk for adenoma/adenocarcinoma than entire females when mammary tumours were excluded.

Table 2 Risk of developing the most common tumour types, comparing sexes and sampling methods. Statistically significant results are in bold. The number of observations was: [1] 126,692; [2] 27,753

Tumour type	Odds ratios and [95% confidence intervals] for females compared to males (OR=1) in samples collected with all methods [1]	post mortem [2]
Adenoma, adenocarcinoma	**1.337 [1.318, 1.356]**	**1.106 [1.075, 1.137]**
Fibroma, fibrosarcoma	**0.904 [0.878, 0.930]**	1.081 [0.966, 1.211]
Hemangioma, hemangiosarcoma	**0.889 [0.862, 0.917]**	**0.908 [0.842, 0.979]**
Lymphoma	**0.953 [0.929, 0.977]**	0.968 [0.926, 1.011]
Mast cell tumour	1.005 [0.984, 1.026]	0.982 [0.874, 1.103]
Melanocytic tumour	**0.843 [0.820, 0.867]**	0.969 [0.843, 1.115]
Osteoma, osteosarcoma	1.004 [0.959, 1.052]	1.031 [0.949, 1.121]
Squamous cell carcinoma	**0.888 [0.856, 0.922]**	**0.784 [0.686, 0.896]**

Table 3 Risk of developing the most common tumour types, comparing castration status and sampling methods. Statistically significant results are in bold. The number of observations was: [1] 43,006; [2] 7,357; [3] 46,387; [4] 6,144

	Neutered males compared to intact males (OR=1)		Neutered females compared to intact females (OR=1)	
	in ex vivo and post mortem samples[1]	in post mortem samples[2]	in ex vivo and post mortem samples[3]	in post mortem samples[4]
Tumour type	**OR & [95%CI]**	**OR & [95%CI]**	**OR & [95%CI]**	**OR & [95%CI]**
Adenoma, adenocarcinoma	**1.384 [1.218, 1.573]**	**1.730 [1.339, 2.237]**	**0.650 [0.604, 0.699]**	1.183 [0.967, 1.446]
Fibroma, fibrosarcoma	1.181 [0.984, 1.417]	0.824 [0.361, 1.880]	**1.183 [1.010, 1.386]**	1.128 [0.559, 2.276]
Hemangioma, hemangiosarcoma	0.995 [0.832, 1.188]	1.005 [0.665, 1.519]	**1.610 [1.374, 1.886]**	**2.438 [1.606, 3.703]**
Lymphoma	**1.150 [1.006, 1.315]**	**1.558 [1.130, 2.150]**	**1.349 [1.194, 1.525]**	**2.295 [1.694, 3.111]**
Mast cell tumour	**1.150 [1.008, 1.313]**	**3.461 [1.515, 7.910]**	**1.190 [1.080, 1.312]**	**2.980 [1.355, 6.551]**
Melanocytic tumour	0.962 [0.817, 1.133]	0.868 [0.251, 3.002]	**1.407 [1.216, 1.627]**	**4.425 [1.619, 12.094]**
Osteoma, osteosarcoma	**1.555 [1.218, 1.985]**	**2.022 [1.151, 3.554]**	1.210 [0.982, 1.491]	1.420 [0.887, 2.275]
Squamous cell carcinoma	0.771 [0.588, 1.010]	**3.811 [1.515, 9.585]**	**1.287 [1.051, 1.576]**	1.969 [0.502, 7.719]

Table 4 Risk of developing a tumour in the most common locations, comparing sexes and sampling methods. Significant results in bold. The number of observations was: [1] 126,692; [2] 27,753

	Females compared to males (OR=1)	
	ex vivo and post mortem samples[1]	post mortem samples[2]
Tumour location	**OR & [95%CI]**	**OR & [95%CI]**
Skin	**0.895 [0.886, 0.905]**	0.964 [0.902, 1.029]
Mammary gland	**3.264 [3.163, 3.369]**	**4.115 [3.486, 4.858]**
Soft tissues	**1.027 [1.011, 1.043]**	0.930 [0.886, 0.975]
Blood, hematopoietic system	**0.912 [0.880, 0.946]**	0.982 [0.930, 1.038]
Neoplasia of bones, joints, cartilage	0.975 [0.936, 1.016]	0.961 [0.892, 1.035]
Endocrine gland	0.996 [0.951, 1.043]	**1.089 [1.032, 1.15]**
Gastrointestinal tract	**0.741 [0.726, 0.756]**	1.005 [0.962, 1.050]
Lymph nodes	**0.923 [0.852, 0.999]**	0.942 [0.837, 1.060]
Oral cavity, pharynx	**0.954 [0.911, 0.999]**	0.964 [0.846, 1.097]
Respiratory system, intrathoracic organs	**0.948 [0.914, 0.982]**	1.024 [0.979, 1.071]
Urinary organs	1.034 [0.965, 1.108]	1.059 [0.951, 1.178]
Unspecified location	**1.032 [1.016, 1.047]**	0.968 [0.936, 1.001]

Table 5 Risk of developing a tumour in the most common locations, comparing castration status and sampling methods. Significant results are in bold. The number of observations was: [1] 43,006; [2] 7,357; [3] 46,387; [4] 6,144.

	Neutered males vs. intact males (OR=1)		Neutered females vs. intact females (OR=1)	
	in ex vivo and post mortem samples[1]	in post mortem samples[2]	in ex vivo and post mortem samples[3]	in post mortem samples[4]
Tumour location	**OR & [95%CI]**	**OR & [95%CI]**	**OR & [95%CI]**	**OR & [95%CI]**
Skin	**1.088 [1.020, 1.161]**	**2.303 [1.473, 3.601]**	**1.208 [1.146, 1.274]**	**2.226 [1.637, 3.028]**
Mammary gland	1.099 [0.842, 1.434]	0.639 [0.077, 5.317]	**0.411 [0.383, 0.440]**	**0.574 [0.408, 0.806]**
Soft tissues	**1.352 [1.247, 1.466]**	1.169 [0.843, 1.621]	**1.278 [1.196, 1.366]**	**2.226 [1.637, 3.028]**
Blood, hematopoietic system	**1.385 [1.069, 1.795]**	**1.974 [1.248, 3.123]**	**1.549 [1.208, 1.986]**	**1.970 [1.251, 3.102]**
Bones, joints, cartilage	**1.492 [1.203, 1.850]**	1.475 [0.881, 2.470]	**1.258 [1.043, 1.517]**	1.136 [0.714, 1.807]
Endocrine gland	**1.563 [1.159, 2.106]**	**1.705 [1.155, 2.516]**	1.262 [0.965, 1.650]	1.101 [0.790, 1.535]
Gastrointestinal tract	1.124 [0.999, 1.265]	**1.579 [1.178, 2.118]**	**1.472 [1.296, 1.672]**	**1.975 [1.524, 2.558]**
Lymph nodes	1.551 [1.000, 2.408]	**2.318 [1.035, 5.195]**	1.105 [0.719, 1.700]	1.137 [0.465, 2.778]
Other male sexual organs (penis, prostate gland, scrotum)	1.279 [0.875, 1.870]	1.729 [0.990,3.020]	no observations	no observations
Other female sexual organs (vagina, uterus, ovary)	no observations	no observations	1.012 [0.747, 1.370]	**0.332 [0.127, 0.870]**
Oral cavity, pharynx	1.267 [0.998, 1.608]	0.358 [0.085, 1.517]	**1.348 [1.094, 1.661]**	**4.733 [2.009, 11.152]**
Respiratory system, intrathoracic organs	**1.498 [1.176, 1.909]**	**1.738 [1.306, 2.313]**	**1.554 [1.271, 1.900]**	**1.784 [1.402, 2.271]**
Urinary organs	1.419 [0.894, 2.251]	1.837 [0.947, 3.566]	**1.695 [1.203, 2.388]**	**2.656 [1.565, 4.508]**
Unspecified location	**1.133 [1.042, 1.233]**	**1.649 [1.275, 2.132]**	1.005 [0.939, 1.075]	**1.803 [1.441, 2.254]**

Discussion

The exceptionally large data set of the Swiss Canine Cancer Registry allowed multiple logistic regression, which was not always possible in the case of other registries and renders comparisons difficult. However, the datasets may be biased over time and further confounders could substantially influence the results. To overcome such influences specifically and to raise sensitivity, more general diagnostic terms were used. Further obstacles to comparison are typical issues related to the reproducibility of diagnoses in pathology, due to criteria for certain diagnoses changing over time and to the clearly subjective factor in histopathological diagnoses (Brønden *et al.*, 2007; Pospischil and Folkers, 2015). In this study, the influence of different time periods on techniques and state of the art in tumour diagnoses was taken into account by including the year of diagnosis as a variable in the statistical evaluation.

For the sake of simplicity only findings determined to be significant in the present work will be discussed below, while discussion of previously described results not confirmed by the present analysis will be omitted.

Adenoma/adenocarcinoma was the most frequent tumour diagnosis in dogs. Its relative proportion in total tumour diagnoses dropped from 40.6% in 1980 to 12.3% in 2008. In 1980, 92.80% of all examined canine patients (n = 2,194) were entire. However, the relative proportion

of entire animals decreased to 55.6% of total patients (*n* = 7,879) in 2008. Since over 60% of the adenomas/adenocarcinomas were found in the sexual organs, the increasing tendency to neuter dogs could be one reason for the decrease in relative frequency of adenoma/adenocarcinoma. A similar tendency was observed for canine mammary cancers in Italy by Merlo *et al.* (2008). Another aspect is the refinement in diagnostics over time, leading to a broader diversity of tumour diagnoses.

The relative frequency of mast cell tumours, melanocytic tumours and haemangioma/haemangiosarcoma rose fairly constantly from 1955 to 2008. Since neutered female dogs are more frequently affected by these tumour types, the increase in neutering frequency over time might be partly responsible for this development.

Vascellari *et al.* (2009) reported a frequency of 3% for canine lymphomas in the animal tumour registry of two provinces in Northern Italy between 2005 and 2008, which is comparable with our data (4.88% lymphomas).

The relative frequency of fibroma/fibrosarcoma increased from 6.52% in 1955 to 10.76% in 1996 and decreased to 5.41% in 2008. These results are in contrast with the increase in feline fibroma/fibrosarcoma (20%) observed in Switzerland in the 1990s (Graf *et al.*, 2016). However, in cats a strong connection between vaccination and the development of sarcomas at sites of injection is under discussion (Henry, 2013). Such a connection has not been observed consistently in dogs.

The peaks in the relative frequency of tumour types between 1996 and 1999 were due to very high numbers of the respective tumours in the data sent in by the Vetsuisse Faculty Institut für Tierpathologie, Bern (ITPA). It is likely that these sudden increases were artificially generated by tumour studies in the institute. This is an example of factors that can skew tumour frequencies in the present study setting.

It is a well-known fact that overall tumour risk increases with age. In our data this was confirmed for adenoma/adenocarcinoma, melanocytic tumours and squamous cell carcinoma. Interestingly, the following tumour types in our study showed a frequency pattern deviating from that described above. The lymphoma risk peaked at 6 years of age. This finding is comparable with results of an Italian study (Merlo *et al.*, 2008) but contradicts data from another study from Italy, which did not, however, perform multivariate statistics (Vascellari *et al.*, 2009). There was no clear age-related incidence of haemangioma/haemangiosarcoma and mast cell tumour in patients >5 years of age. This could indicate the influence of the genetic background or other external factors.

Findings related to the effect of neutering status on tumour development were partly dependent on the examination method, specifically on whether the animal was dead or alive at the time of diagnosis. Overall tumour incidence in post-mortem samples was higher in neutered than in entire dogs, suggesting bias through investigation of mammary glands and testes in ex-vivo materials. The difference of the odds ratios for specific tumours in female dogs compared with male dogs was small in both sampling groups. Females were at a lower risk for haemangioma/haemangiosarcoma and squamous cell carcinoma compared with males, while they had a 33.7% higher risk for adenoma/adenocarcinoma overall. In post-mortem samples the risk was only 10.6% higher for females than for males. However, when the neutering status was taken into consideration, the difference between the sampling groups was higher, confirming the suggested bias mentioned above.

Neutered dogs were shown to have a higher risk of developing tumours in various locations other than the sexual organs, which is consistent with data from other studies (Brønden *et al.*, 2010; Torres de la Riva *et al.*, 2013; Zink *et al.*, 2014). Other authors report that tumour risk in the mammary glands in entire dogs is higher than in neutered animals, a finding supported by our data (MacVean *et al.*, 1978; Porrello *et al.*, 2006; Brønden *et al.*, 2010; Henry, 2013).

Neutered male and female dogs showed higher odds ratios for lymphoma and mast cell tumour. Neutered female dogs additionally showed higher odds ratios for melanocytic tumours and haemangioma/haemangiosarcomas, as did neutered male dogs for adenoma/adenocarcinoma and osteoma/osteosarcoma. These correlations need to be validated by future research.

In the present study, breed predispositions for neoplasia in general, arranged in descending order, were recorded in boxers, cocker spaniels, poodles, Swiss mountain dogs, dachshunds, setters, schnauzers and retrievers. In contrast, great Danes, bulldogs, West Highland white terriers, Parson Jack Russell terriers, rottweiler, dobermans, collies, shepherds and Yorkshire terriers showed a lower risk of developing a tumour compared with crossbreds.

Other authors report the boxer, the flat coated retriever and the golden retriever (subsets of the category of retriever in our study), the Bernese mountain dog and the Saint Bernard (subsets of the Swiss mountain dog) and the giant schnauzer (a subset of schnauzer) as being more susceptible to tumour development (Brønden *et al.*, 2010; Bell *et al.*, 2012; Dobson, 2013). German shepherd dogs were at a lower risk of tumour development in the Danish Veterinary Cancer Registry (Brønden *et al.*, 2010). These findings are roughly confirmed by our study, taking into account the differences in breed allocation.

For a better overview and clinical relevance we hereafter only discuss outstanding results of the influence of breed on the development of some specific tumours.

The boxer had an almost five times higher risk (OR 4.926 [CI = 4.343, 5.587]) of developing a mast cell tumour and a 1.85 times higher risk of haemangioma/haemangiosarcoma (OR 1.850 [CI = 1.506, 2.261]). Similar findings have been described in the literature (Misdorp, 2004; Gough and Thomas, 2010).

The Schnauzer was two times more susceptible for melanocytic tumour and seven times more susceptible for squamous cell carcinoma than crossbreds. Melanocytic tumour is known to occur more frequently in dogs with darkly pigmented skin or oral mucosa (e.g. schnauzers) (Gough and Thomas, 2010; Dobson 2013). The odds ratio for squamous cell carcinoma in the schnauzer was higher than expected, which might indicate either a genetic or an environmental factor associated with the geographical area from which the samples originate. Gough and Thomas (2010) report a predisposition of the schnauzer for squamous cell carcinoma of the digit in a case series.

The shepherd had higher odds ratios (OR 1.806 [CI = 1.518, 2.150]) of developing a haemangioma/haemangiosarcoma, which is consistent with previous reports (Gough and Thomas, 2010).

The rottweiler (OR 3.321 [CI = 2.321, 4.752]) and the great Dane (OR 1.936 [CI = 1.248, 3.003]) had a higher risk of developing an osteoma/osteosarcoma. This tendency has also been reported in the literature (Gough and Thomas, 2010). Reported risk factors for canine osteosarcoma are high weight, high height, early neutering and breed predisposition (e.g. Irish wolfhound, Saint Bernard, great Dane, rottweiler, Irish setter, doberman pinscher, golden retriever, Labrador retriever and Leonberger) (Porrello *et al.*, 2006; Butler *et al.*, 2013). Genetic factors have been observed to differentiate rottweilers and golden retrievers with regard to the incidence of spontaneous appendicular osteosarcoma, independent of sex, age and histological classification (Thomas *et al.*, 2009). The most significant difference was the deletion of the *WT1* gene in 48% of the rottweiler tumour cases, while this did not occur in any of the golden retrievers. A recent study suggests that 'weight-bearing stress during the period of high proliferative activity in the long bones associated with growth may increase the risk of canine primary bone cancer' (Anfinsen *et al.*, 2015).

There was, in the present study, no significant difference between mixed breeds and the examined breeds/breed categories with regard to general cancer risk, which contrasts with the report of Brønden *et al.* (2007), who showed a twofold increased risk of developing tumours for pure breeds compared with mixed breeds. Vascellari *et al.* (2009), in addition, described the estimated crude annual incidence rate for malignant tumours as twofold higher in purebred dogs than in crossbreed dogs (Vascellari *et al.*, 2009). Different data collecting or breed definition standards might be the reason for these contradictory results. Since the declaration of breed is usually provided by the owner of the dog, it is necessary to avoid future uncertainties related to breed declaration through genetic testing. Today, the examination of the genome of dogs and the identification of single nucleotide polymorphism (SNP) haplotypes allows the classification of dog breeds on the basis of genetic relationship (Vonholdt *et al.*, 2010). This will be addressed in a follow-up study. Additionally, the breed-related risks found in the present study were confirmed

through analysis of the newest data from the Swiss Canine Cancer Registry of 2009 to 2013 (data not shown).

Small breeds were at a higher risk of developing tumours of the mammary gland and the endocrine glands than large breeds. The following tumour locations were less likely in small breeds than in large breeds: the respiratory system and intrathoracic organs, the blood and hemopoietic system, soft tissues, skin, retroperitoneum and peritoneum, other female sexual organs, bones, joints and articular cartilage. Contrasting findings, such as a lower malignant mammary tumour incidence in small breed dogs, are suggested by Itoh *et al.* (2005). Further investigations will be necessary to verify those results. The unexpectedly high risk of developing tumours of the mammary glands for small breeds in our data could be explained by their tendency to have shorter sexual cycles (Arnold-Gloor *et al.*, 2011) and therefore increased exposure to sex hormones during oestrus.

The breeds/breed categories with lower risk of developing osteoma/osteosarcoma were breeds of small body size, with the exception of poodles and schnauzers, which show varying body sizes. These results suggest that size and castration are predisposing factors for skeletal tumours.

The large sample size in the present study allowed a detailed insight into the occurrence of the most common tumour diagnoses over time and into the influences of age, breed, body size, sex and neutering status on canine tumour development. Through the inclusion of influencing variables in the statistics, bias factors such as the examination method or the year of diagnosis were controlled for. Naturally, not all environmental tumour risk factors were recorded in this retrospective cancer registry and therefore could not be included in the statistical evaluation. The clinical relevance still has to be elucidated.

In many cases, the results of the analysis of the Swiss Canine Cancer Registry confirm the findings of other authors. In some cases, the results were unique or contradicted other studies, implying that further investigations are necessary.

The reproducibility of cancer epidemiological studies is greatly affected by the absence of international standards for veterinary cancer registries (Brønden *et al.*, 2007). In addition, the lack of guidelines leads to enormous differences in data collection and consolidation methods among existing veterinary cancer registries (Brønden *et al.*, 2007; Vascellari *et al.*, 2009). To achieve a more accurate comparison it is crucial to define international de jure standards for veterinary cancer registries. It is desirable to collect even more primary information from the canine tumour patient for further epidemiological studies of canine cancer, such as type of treatment, diet, age at neutering, obesity (body mass index) and body size, the presence of other diseases, vaccination status and environmental factors (e.g. exposure to cigarette smoke and other husbandry conditions, daily exercise).

6. Supplemental material

Table 1 Distribution of tumour diagnoses. The tumour diagnoses analyzed in the present study are printed in bold.

Tumour	Frequency
Adenoma, adenocarcinoma (ICD-O 8140)	**12,293 (18.09%)**
Complex mixed tumor, neoplasia of stroma (ICD-O 8940)	6,465 (9.52%)
Mast cell tumour (ICD-O 9740)	**4,415 (6.50%)**
Lipoma (ICD-O 8850)	3,522 (5.18%)
Unclassified neoplasm (ICD-O 8000)	2,775 (4.08%)
Lymphoma (ICD-O 9590, 9591, 9700)	**2,955 (4.35%)**
Melanocytic tumour (ICD-O 8720, 8730)	**2,466 (3.63%)**
Adenocarcinoma of anal glands (ICD-O 8215)	2,420 (3.56%)
Soft tissue tumour (ICD-O 8800)	2,315 (3.41%)
Fibroma, fibrosarcoma (ICD-O 8810, 8812)	**2,309 (3.40%)**
Hemangioma/hemangiosarcoma (ICD-O 9120)	**1,904 (2.80%)**
Histiocytoma (ICD-O 8831)	1,686 (2.48%)
Epithelial tumor (ICD-O 8010)	1,677 (2.47%)
Dermatofibroma, dermatofibrosarcoma (ICD-O 8832)	1,585 (2.33%)
Sebaceous adenoma, sebaceous adenocarcinoma (ICD-O 8410)	1,456 (2.14%)
Hemangiopericytoma (ICD-O 9150)	1,256 (1.85%)
Squamous cell carcinoma (ICD-O 8070, 8071, 8078)	**1,324 (1.95%)**
Trichoepithelioma (ICD-O 8100)	1,116 (1.64%)
Epithelioma (ICD-O 8011)	958 (1.41%)
Papillary carcinoma (ICD-O 8050)	871 (1.28%)
Osteoma/osteosarcoma (ICD-O 9180)	**842 (1.24%)**
Hemangioendothelioma, hemangioendotheliosarcoma (ICD-O 9130)	622 (0.92%)
Seminoma (ICD-O 9061)	618 (0.91%)
Spindle cell sarcoma (ICD-O 8801)	547 (0.81%)
Leiomyoma (ICD-O 8890)	538 (0.79%)
Plasmacytoma (ICD-O 9731)	520 (0.77%)
Pilomatrixoma (ICD-O 8110)	503 (0.74%)
Leydig cell tumor (ICD-O 8650)	450 (0.66%)
Sweat gland adenoma, sweat gland adenocarcinoma (ICD-O 8400)	427 (0.63%)
Sertoli cell adenoma, sertoli cell carcinoma (ICD-O 8640)	423 (0.62%)
Basal cell tumour	413 (0.61%)
Langerhans cell histiocytosis (ICD-O 9751)	356 (0.52%)
Secretory carcinoma of breast (ICD-O 8502)	329 (0.48%)
Adenomatous polyp, adenocarcinoma in adenomatous polyp (ICD-O 8210)	321 (0.47%)
Carcinoma, anaplastic type (ICD-O 8021)	296 (0.44%)
Malignant histiocytosis (ICD-O 9750)	287 (0.42%)
Multifocal superficial basal cell carcinoma (ICD-O 8091)	231 (0.34%)
Myxoma, myxosarcoma (ICD-O 8840)	209 (0.31%)
Ameloblastic fibroma, ameloblastic fibrosarcoma (ICD-O 9330)	197 (0.29%)
Adenocarcinoma with squamous metaplasia (ICD-O 8570)	190 (0.28%)
Magnocellular nevus (ICD-O 8726)	185 (0.27%)
Leukemia (ICD-O 9800)	178 (0.26%)

Chondroma, chondrosarcoma (ICD-O 9220)	168 (0.25%)
Adrenal cortical adenoma, adrenal cortical adenocarcinoma (ICD-O 8370)	168 (0.25%)
Transitional cell papilloma, transitional cell carcinoma (ICD-O 8120)	168 (0.25%)
Hepatoma, hepatocarcinoma (ICD-O 8170)	155 (0.23%)
Papillary adenoma, adenocarcinoma (ICD-O 8260)	112 (0.16%)
Meningioma (ICD-O 9530)	111 (0.16%)
Adamantinoma of the jaw (ICD-O 9261)	103 (0.15%)
Fibrolipoma, liposarcoma (ICD-O 8851)	103 (0.15%)
Chemodectoma (ICD-O 8693)	101 (0.15%)
Fibrous histiocytoma (ICD-O 8830)	98 (0.14%)
Thymoma (ICD-O 8580)	96 (0.14%)
Round cell sarcoma (ICD-O 8803)	95 (0.14%)
Fibromyxoma, fibromyxosarcoma (ICD-O 8811)	93 (0.14%)
Sertoli-Leydig cell tumor (ICD-O 8631)	92 (0.14%)
Histiocytic sarcoma (ICD-O 9755)	88 (0.13%)
Fibroepithelial basal cell carcinoma (ICD-O 8093)	86 (0.13%)
Glioma (ICD-O 9380)	83 (0.12%)
Intracystic papillary adenoma, intracystic papillary adenocarcinoma (ICD-O 8504)	79 (0.12%)
Granulosa cell tumour, granulosa cell carcinoma (ICD-O 8620)	75 (0.11%)
Spindle cell carcinoma (ICD-O 8032)	72 (0.11%)
Neurilemmoma (ICD-O 9560)	69 (0.10%)
Other tumours (frequency < 64, percentage < 0.1%)	1,278 (1.86%)
All tumour diagnoses (ICD-O 8000 – 9930)	67,943 (100%)

Table 2 The distribution of tumour locations in male dogs (all examination methods).

Tumour location	Number and relative percentage of occurrences in intact males		castrated males		all males	
Skin ICD-O C 44	5,181	(34.81%)	1,578	(35.64%)	6,759	(35.00%)
Unspecified location ICD-O C 80	2,486	(16.70%)	849	(19.18%)	3,335	(17.27%)
Soft tissues ICD-O C 49	2,378	(15.98%)	954	(21.55%)	3,332	(17.25%)
Gastrointestinal tract ICD-O C 16-26.8	1,361	(9.14%)	386	(8.72%)	1,747	(9.05%)
Testes ICD-O C 62	1,360	(9.14%)	0	(0.00%)	1,360	(7.04%)
Other male sexual organs (penis, prostate gland, scrotum) ICD-O C 60, 61, 63.2	127	(0.85%)	37	(0.84%)	164	(0.85%)
Neoplasia of bones, joints, cartilage ICD-O C40-41	332	(2.23%)	122	(2.76%)	454	(2.35%)
Oral cavitiy, pharynx ICD-O 2.9-11	306	(2.06%)	94	(2.12%)	400	(2.07%)
Mammary gland ICD-O C 50	323	(2.17%)	71	(1.60%)	394	(2.04%)
Respiratory system, intrathoracic organs ICD-O C 30-39	292	(1.96%)	97	(2.19%)	389	(2.01%)
Blood, hematopoietic system ICD-O C42	213	(1.43%)	85	(1.92%)	298	(1.54%)
Endocrine gland ICD-O C 73-75	203	(1.36%)	64	(1.45%)	267	(1.38%)
Lymph nodes ICD-O C 77	95	(0.64%)	29	(0.66%)	124	(0.64%)
Urinary organs ICD-O C 67-68	81	(0.54%)	26	(0.59%)	107	(0.55%)
Other tumour locations	146	(0.98%)	35	(0.79%)	65	(0.34%)
All tumour locations ICD-O C 2.9-80	14,884	(100%)	4,427	(100%)	19,311	(100%)

Table 3 The distribution of tumour locations in male dogs (post mortem samples).

Tumour location	Number and relative percentage of occurrences in intact males		castrated males		all males	
Unspecified location ICD-O C 80	316	(16.34%)	90	(19.69%)	406	(16.98%)
Gastrointestinal tract ICD-O C 16-26.8	266	(13.75%)	66	(14.44%)	332	(13.89%)
Respiratory system, intrathoracic organs ICD-O C 30-39	231	(11.94%)	73	(15.97%)	304	(12.71%)
Soft tissues ICD-O C 49	229	(11.84%)	50	(10.94%)	279	(11.67%)
Testes ICD-O C 62	187	(9.67%)	0	(0.00%)	187	(7.82%)
Other male sexual organs (penis, prostate gland, scrotum) ICD-O C 60, 61, 63.2	65	(3.36%)	18	(3.94%)	83	(3.47%)
Endocrine gland ICD-O C 73-75	146	(7.55%)	37	(8.10%)	183	(7.65%)
Skin ICD-O C 44	108	(5.58%)	30	(6.56%)	138	(5.77%)
Neoplasia of bones, joints, cartilage ICD-O C40-41	93	(4.81%)	20	(4.38%)	113	(4.73%)
Blood, hematopoietic system ICD-O C42	69	(3.57%)	29	(6.35%)	98	(4.10%)
Urinary organs ICD-O C 67-68	44	(2.28%)	13	(2.84%)	57	(2.38%)
Oral cavitiy, pharynx ICD-O 2.9-11	53	(2.74%)	2	(0.44%)	55	(2.30%)
Lymph nodes ICD-O C 77	42	(2.17%)	9	(1.97%)	51	(2.13%)
Mammary gland ICD-O C 50	12	(0.62%)	1	(0.22%)	13	(0.54%)
Other tumour locations	73	(3.77%)	19	(4.16%)	92	(3.85%)
All tumour locations ICD-O C 2.9-80	1,934	(100%)	457	(100%)	2,391	(100%)

Table 4 The distribution of tumour locations in female dogs in ex vivo and post mortem samples.

Tumour location	Number and relative percentage of occurrences in intact females		castrated females		all females	
Skin ICD-O C 44	4,062	(26.89%)	3,152	(33.06%)	7,214	(29.28%)
Mammary gland ICD-O C 50	4,544	(30.08%)	1,191	(12.49%)	5,735	(23.28%)
Unspecified location ICD-O C 80	2,355	(15.59%)	1,702	(17.85%)	4,057	(16.47%)
Soft tissues ICD-O C 49	2,108	(13.96%)	1,908	(20.01%)	4,016	(16.3%)
Gastrointestinal tract ICD-O C 16-26.8	594	(3.93%)	482	(5.06%)	1,076	(4.37%)
Neoplasia of bones, joints, cartilage ICD-O C40-41	270	(1.79%)	208	(2.18%)	478	(1.94%)
Respiratory system, intrathoracic organs ICD-O C 30-39	239	(1.58%)	204	(2.14%)	443	(1.80%)
Oral cavitiy, pharynx ICD-O 2.9-11	211	(1.40%)	170	(1.78%)	381	(1.55%)
Blood, hematopoietic system ICD-O C42	138	(0.91%)	136	(1.43%)	274	(1.11%)
Endocrine gland ICD-O C 73-75	173	(1.15%)	100	(1.05%)	273	(1.11%)
Other female sexual organs (vagina, uterus, ovary) ICD-O C 52-57	133	(0.88%)	69	(0.72%)	202	(0.82%)
Urinary organs ICD-O C 67-68	76	(0.50%)	71	(0.74%)	147	(0.60%)
Lymph nodes ICD-O C 77	62	(0.41%)	37	(0.39%)	99	(0.40%)
Other tumour locations	140	(0.93%)	104	(1.09%)	244	(0.99%)
All tumour locations ICD-O C 2.9-80	15,105	(100%)	9,534	(100%)	2,4639	(100%)

Table 5 The distribution of tumour locations in female dogs in post mortem samples.

Tumour location	Number and relative percentage of occurrences in intact females		castrated females		all females	
Unspecified location ICD-O C 80	209	(15.13%)	171	(19.81%)	380	(16.93%)
Respiratory system, intrathoracic organs ICD-O C 30-39	175	(12.67%)	146	(16.92%)	321	(14.30%)
Mammary gland ICD-O C 50	267	(19.33%)	45	(5.21%)	312	(13.90%)
Gastrointestinal tract ICD-O C 16-26.8	168	(12.17%)	126	(14.6%)	294	(13.10%)
Endocrine gland ICD-O C 73-75	140	(10.14%)	59	(6.84%)	199	(8.87%)
Soft tissues ICD-O C 49	101	(7.31%)	96	(11.12%)	197	(8.78%)
Skin ICD-O C 44	63	(4.56%)	44	(5.10%)	107	(4.77%)
Neoplasia of bones, joints, cartilage ICD-O C40-41	62	(4.49%)	30	(3.48%)	92	(4.10%)
Blood, hematopoietic system ICD-O C42	46	(3.33%)	42	(4.87%)	88	(3.92%)
Urinary organs ICD-O C 67-68	31	(2.24%)	35	(4.06%)	66	(2.94%)
Brain, meninges, other parts of CNS ICD-O C 70-72	26	(1.88%)	27	(3.13%)	53	(2.36%)
Other female sexual organs (vagina, uterus, ovary) ICD-O C 52-57	39	(2.82%)	5	(0.58%)	44	(1.96%)
Lymph nodes ICD-O C 77	22	(1.59%)	8	(0.93%)	30	(1.34%)
Oral cavitiy, pharynx ICD-O 2.9-11	13	(0.94%)	17	(1.97%)	30	(1.34%)
Other tumour locations	19	(1.36%)	12	(1.39%)	31	(1.38%)
All tumour locations ICD-O C 2.9-80	1,381	(100%)	863	(100%)	2,244	(100%)

Table 6 Risk of developing the most common tumour types, comparing castrated females and intact females and sampling methods. Tumours of the mammary gland were excluded. Statistically significant results are in bold. The number of observations was: [1]40,652; [2] 5,832.

	Neutered females compared to intact females (OR=1)	
	in ex vivo and post mortem samples[1]	in post mortem samples[2]
Tumour type	**OR & [95%CI]**	**OR & [95%CI]**
Adenoma, adenocarcinoma	**0.889 [0.795, 0.994]**	**1.522 [1.218, 1.903]**
Fibroma, fibrosarcoma	1.046 [0.893, 1.226]	1.155 [0.568, 2.351]
Hemangioma, hemangiosarcoma	**1.425 [1.217, 1.670]**	**2.379 [1.565, 3.618]**
Lymphoma	**1.277 [1.30, 1.443]**	**2.293 [1.688, 3.115]**
Mast cell tumour	1.066 [0.967, 1.175]	**2.926 [1.324, 6.465]**
Melanocytic tumour	**1.243 [1.075, 1.439]**	**4.398 [1.597, 12.112]**
Osteoma, osteosarcoma	1.121 [0.907, 1.386]	1.315 [0.818, 2.114]
Squamous cell carcinoma	1.125 [0.917, 1.379]	1.953 [0.495, 7.696]

Table 7 Risk of developing a tumour in the most common locations, comparing castrated females and intact females and sampling methods. Tumours of the mammary gland were excluded. Significant results are in bold. The number of observations was: [1] 40,652; [2] 5,832.

	Neutered females vs. intact females (OR=1)	
	in ex vivo and post mortem samples[1]	in post mortem samples[2]
Tumour location	**OR & [95%CI]**	**OR & [95%CI]**
Skin	0.997 [0.946, 1.051]	**1.823 [1.188, 2.796]**
Soft tissues	**1.189 [1.119, 1.271]**	**2.182 [1.603, 2.972]**
Blood, hematopoietic system	**1.497 [1.168, 1.918]**	**1.924 [1.219, 3.035]**
Bones, joints, cartilage	1.120 [0.929, 1.351]	1.113 [0.699, 1.772]
Endocrine gland	1.235 [0.945, 1.613]	1.078 [0.772, 1.504]
Gastrointestinal tract	**1.298 [1.143, 1.475]**	**1.939 [1.495, 2.515]**
Lymph nodes	1.000 [0.650, 1.536]	1.117 [0.456, 2.739]
Other female sexual organs (vagina, uterus, ovary)	0.835 [0.617, 1.130]	**0.324 [0.124, 0.850]**
Oral cavity, pharynx	1.105 [0.897, 1.361]	**4.720 [1.983, 11.232]**
Respiratory system, intrathoracic organs	**1.520 [1.245, 1.857]**	**1.742 [1.367, 2.219]**
Urinary organs	**1.577 [1.120, 2.220]**	**2.606 [1.532, 4.434]**
Unspecified location	0.952 [0.890, 1.018]	**1.763 [1.408, 2.207]**

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Lebenslauf

Persönliche Daten

Vorname Name:	Grüntzig, Katrin
Geburtsdatum:	22.05.1968
Geburtsort:	Heidelberg, Deutschland
Nationalität:	Deutsch und Schweiz
Heimatort:	Zürich, Schweiz

Schulausbildung

08.1974 – 06.1978	Geschwister-Scholl-Grundschule, Heidelberg, Deutschland
08.1978 – 06.1987	Bunsengymnasium, Heidelberg, Deutschland
15.05.1987	Abitur, Bunsengymnasium, Heidelberg, Deutschland

Studium

1987 - 1993	Veterinärmedizinstudium, Justus-Liebig-Universität Giessen, Deutschland
02.09. 1993	Approbation Tierärztin

Dissertation

09.2011 – 04. 2016	Anfertigung der Dissertation unter Leitung von Prof. em. Dr. med. vet. Andreas Pospischil am Institut für Veterinärpathologie der Vetsuisse-Fakultät Universität Zürich, Direktor Prof. Dr. vet. med. Anja Kipar

Anstellungen

03. 2009 - 04. 2011	Hospitanz + Praxisvertretungen, Dr. med. vet. A. Maurer, Kleintierpraxis Effretikon
05. 2010 - 12. 2010	Assistenztierärztin, Schwangerschaftsvertretung, Gross - und Kleintierpraxis Dres. Rohner und Huber, Birmensdorf
11. 2011 - 04. 2012	Internship, Bessy`s Kleintierklinik, Regensdorf
07. 2012 - 12. 2014	Wissenschaftliche Mitarbeiterin, Collegium Helveticum, Zürich
01. 2015 - 05. 2016	Assistenztierärztin, Gross - und Kleintiere Tierarztpraxis in der Ebni, Neftenbach

Weiterbildungen Tiermedizin

2009 - 2011	Homöopathie Grundausbildung, Universität Zürich
2009 - 2015	Akupunktur für Kleintiere, Chi-Institut Madrid
2010 - 2011	Wiedereinstiegskurs für Tierärztinnen (GST), Bessy`s Kleintierklinik
2016 - 2016	Akupunktur für Pferde und Kleintiere, Chi-Institut Madrid